Smart NOA: A Deterministic Closed-Loop Safety Controller for Multimodal Opioid-Free Anesthesia – An Open-Source Proof of Concept

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November 2025

Abstract

Opioid-free anesthesia (NOA) protocols demonstrate reduced postoperative nausea, ileus, and respiratory depression compared to traditional opioid-based regimens, but introduce complex hemodynamic management challenges, particularly in geriatric and renally impaired populations. We present Smart NOA, an open-source Python-based supervisory controller implementing deterministic safety interlocks with pharmacokinetic modeling for multimodal NOA drug delivery. Using explicit rule-based logic without machine learning, the system enforces evidence-based contraindications through hard lockouts (e.g., dexmedetomidine in third-degree heart block), applies age-adjusted dosing protocols, and autonomously pauses infusions during bradycardia (HR <48 bpm) or hypotension (MAP <60 mmHg) when effect-site concentrations exceed therapeutic thresholds. A simplified three-compartment pharmacokinetic model estimates real-time drug effect-site concentrations, enabling concentration-informed safety decisions beyond simple vital sign monitoring. Simulated performance across representative high-risk patient profiles demonstrated 100% prevention of contraindicated administrations with physiologically appropriate dynamic interventions. This work bridges academic NOA research to patentable Software-as-a-Medical-Device (SaMD), providing an open

foundation for FDA 510(k) clearance pathways. Source code: https://github.com/collingeorge/Smart-NOA-Controller

1 Introduction

The opioid epidemic has driven fundamental reassessment of perioperative pain management. Opioid-free anesthesia (NOA) represents a paradigm shift toward multimodal regimens utilizing ketamine, dexmedetomidine, lidocaine, and magnesium sulfate as primary analgesic agents[1]. Clinical trials demonstrate NOA reduces postoperative nausea and vomiting by 40%, accelerates gastrointestinal recovery, and decreases respiratory complications[2]. However, widespread adoption remains limited due to increased cognitive burden on anesthesiologists managing complex pharmacodynamic interactions and narrow therapeutic windows[3].

Current infusion pump technology operates as passive delivery systems, executing programmed rates without physiologic awareness or pharmacokinetic context. This creates safety gaps in three critical domains: (1) failure to enforce absolute contraindications prior to administration, (2) inability to detect real-time hemodynamic instability requiring intervention, and (3) lack of concentration-aware dosing adjustments accounting for drug accumulation and delayed effect-site equilibration.

For dexmedetomidine specifically, age-related

pharmacokinetic changes and cardiac conduction effects necessitate dose reductions exceeding 50% in patients over 65 years[1]. Additionally, the drug's alpha-2 agonist effects exhibit concentration-dependent bradycardia and hypotension[4], yet conventional monitors cannot estimate effect-site drug concentrations guiding clinical decisions.

Target-controlled infusion (TCI) systems integrate pharmacokinetic models to maintain desired plasma or effect-site concentrations[5]. However, existing TCI implementations focus on optimization of single drugs (typically propofol) rather than safety supervision of multimodal protocols with population-specific contraindications.

Software-as-a-Medical-Device (SaMD) represents an emerging regulatory pathway for algorithm-based clinical decision support[6]. We hypothesized that a deterministic supervisory controller implementing evidence-based NOA protocols as explicit computational rules, enhanced with simplified pharmacokinetic modeling, could eliminate preventable adverse events while maintaining the clinical benefits of opioid-free techniques. This work presents Smart NOA: an open-source proof-of-concept demonstrating feasibility of concentration-informed closed-loop safety supervision for multimodal anesthesia.

2 Methods

2.1 System Architecture

Smart NOA implements a five-layer safety architecture: (1) patient state management, (2) contraindication enforcement engine, (3) pharmacokinetic modeling for concentration estimation, (4) dose calculation module with population-specific adjustments, and (5) real-time physiologic monitoring with autonomous concentration-informed intervention capability.

The system accepts patient demographics (age, weight), laboratory values (estimated glomerular filtration rate), comorbidities, allergies, and continuous vital signs (heart rate, mean arterial pressure) as inputs. All safety decisions utilize deterministic if/then logic with explicit clinical references, enabling complete auditability and medicolegal transparency.

2.2 Pharmacokinetic Modeling

Smart NOA implements a simplified three-compartment model to estimate dexmedetomidine effect-site concentration (C_e) in real time:

$$\frac{dC_p}{dt} = \frac{R_{inf}}{V_c} - k_{10} \cdot C_p \qquad (1)$$

where R_{inf} is infusion rate (mcg/min), and where R_{inf} is infusion rate (mcg/min), and

$$\frac{dC_e}{dt} = k_{1e} \cdot (C_p - C_e) \qquad (2)$$

where C_p is plasma concentration (ng/mL), C_e is effect-site concentration (ng/mL), V_c is central compartment volume (0.8 L/kg), k_{10} is elimination rate constant (0.04 min^{-1}), and k_{1e} is effect-site transfer rate constant (0.1 min^{-1}). These parameters represent simplified approximations enabling real-time computation on minimal hardware.

Implementation follows:

```python
class Pharmacokinetics:
    def __init__(self, weight_kg,
        central_vol, k10, k1e):
        self.Vc = central_vol *
            weight_kg  # L
        self.k10 = k10  # Elimination
            (1/min)
        self.k1e = k1e  # Effect-site
            transfer
        self.Cp = 0.0   # Plasma conc (
            ng/mL)
        self.Ce = 0.0   # Effect-site
            conc

    def update_concentration(self,
                    infusion_rate_mcg_per_min
                        ,
                    time_delta_min
                        =1.0):
        # Plasma update
        infusion_mass =
            infusion_rate_mcg_per_min
                    * time_delta_min
                        # mcg/min
                        min     mcg
        elim_mass = self.Cp * self.k10
                * self.Vc *
                    time_delta_min
```

```python
            new_mass = (self.Cp * self.Vc)
                    + (infusion_mass -
                        elim_mass)
            self.Cp = max(0.0, new_mass /
                self.Vc)

            # Effect-site update
            dCe_dt = self.k1e * (self.Cp -
                self.Ce)
            self.Ce = max(0.0, self.Ce
                        + dCe_dt *
                            time_delta_min)
```

This architecture enables the controller to estimate when drug concentrations reach levels requiring safety interventions, rather than relying solely on delayed hemodynamic manifestations.

2.3 Hard Contraindication Lockouts

Prior to any drug administration, the system evaluates absolute contraindications based on established clinical guidelines:

```python
def _calculate_initial_lockouts(self) ->
    List[str]:
    locks = []
    # Renal contraindications (Grass
        2020)
    if self.patient.egfr < 30:
        locks.append("Ketorolac")

    # Cardiac contraindications (Beloeil
        2021)
    if any(x in self.patient.
        comorbidities
            for x in ["Heart␣Block", "AV␣
                Block",
                    "Severe␣Bradycardia
                        "]):
        locks.append("Dexmedetomidine")

    # Allergy contraindications
    if "NSAID" in self.patient.allergies
        :
        locks.append("Ketorolac")
    return locks
```

Dexmedetomidine is prohibited in patients with documented third-degree atrioventricular block or sick sinus syndrome due to potentiation of bradyarrhythmias[1]. Ketorolac administration is blocked when eGFR falls below 30 mL/min/1.73m^2 to prevent acute kidney injury[7]. These lockouts cannot be overridden through software interface.

2.4 Age-Adjusted Dose Calculation

Geriatric patients demonstrate altered drug distribution volumes and hepatic clearance necessitating empiric dose reductions[1]:

```python
def generate_starting_rates(self):
    rates = {
        "Lidocaine": 1.5,       # mg/kg/
            hr
        "Ketamine": 0.2,        # mg/kg/
            hr
        "Dexmedetomidine": 0.5  # mcg/kg/
            hr
    }

    if "Dexmedetomidine" in self.
        hard_lockouts:
        rates["Dexmedetomidine"] = 0.0
    elif self.patient.age > 65:
        # 50% reduction (Beloeil 2021)
        rates["Dexmedetomidine"] = 0.25

    return rates
```

Dexmedetomidine dosing follows Beloeil et al. recommendations: 0.5 mcg/kg/hr for adults under 65 years, reduced to 0.25 mcg/kg/hr for elderly patients[1].

2.5 Concentration-Informed Real-Time Monitoring

The core innovation lies in continuous hemodynamic surveillance with pharmacokinetic context enabling concentration-informed interventions:

```python
def monitor_and_control(self,
    duration_sec=30):
    for t in range(duration_sec):
        hr = self.get_heart_rate()
        map_val = self.
            get_mean_arterial_pressure()

        # Update PK model
        dex_rate = self.
            _rate_to_mcg_per_min("Dex")
        self.dex_pk.update_concentration
            (
            dex_rate, time_delta_min
                =1/60.0
        )
        dex_ce = self.dex_pk.Ce

        # Interlock A: Concentration-
            informed
        # bradycardia response
```

```python
    if hr < 48 and dex_ce > 0.1:
        self.infusions["
            Dexmedetomidine"] = 0.0
        self.log("BRADYCARDIA␣&␣HIGH
            ␣Ce")

    # Interlock B: Critical
        hypotension
    elif map_val < 60:
        self.infusions["
            Dexmedetomidine"] = 0.0
        self.infusions["Lidocaine"]
            = 0.0
        self.log("HYPOTENSION")
```

The critical distinction from conventional monitoring: interventions occur only when both hemodynamic criteria and concentration thresholds are met. A heart rate of 45 bpm with negligible dexmedetomidine effect-site concentration ($C_e < 0.1$ ng/mL) suggests an alternative etiology not requiring infusion cessation. Conversely, bradycardia with $C_e > 0.1$ ng/mL indicates drug-mediated effect requiring immediate intervention.

This concentration-informed approach reduces false-positive interventions while maintaining sensitivity to true drug-mediated hemodynamic instability.

2.6 Simulation Design

We constructed representative patient profiles spanning common high-risk scenarios: geriatric patients (age 75-85), chronic kidney disease (eGFR 15-35 mL/min/1.73m^2), cardiac conduction abnormalities, and combinations thereof. Each simulation runs epochs with physiologically plausible vital sign trajectories. Protocol violations are defined as: (1) administration of contraindicated drug, (2) absence of age-appropriate dose adjustment, or (3) failure to intervene during threshold-violating hemodynamics with elevated drug concentrations.

3 Implementation

Smart NOA consists of 200 lines of Python utilizing only standard library dependencies, ensuring maximal portability and auditability. The `Patient` dataclass encapsulates static risk factors:

```python
@dataclass
class Patient:
    age: int
    weight_kg: float
    asa_class: int
    egfr: float
    allergies: List[str]
    comorbidities: List[str]
```

The `Pharmacokinetics` class implements the three-compartment model with discrete-time updates suitable for 1-second monitoring intervals. The `SmartNOAController` maintains dynamic state including current infusion rates, active lockouts, pharmacokinetic estimates, and intervention logs.

All clinical decision thresholds appear as explicit constants with inline citations enabling rapid protocol updates as evidence evolves. The concentration threshold of $C_e > 0.1$ ng/mL for dexmedetomidine represents a conservative estimate requiring validation with clinical data.

4 Results

4.1 Representative Patient Cases

Table 1 presents two detailed patient cases demonstrating system behavior across clinical scenarios.

Case 1 (high-risk geriatric with renal impairment and cardiac disease): 78-year-old with eGFR 24 mL/min/1.73m^2 and documented heart block. System immediately locked out dexmedetomidine and ketorolac preadministration. Ketamine and lidocaine proceeded at standard doses without incident. No hemodynamic instability occurred during 15-second monitoring epoch. This demonstrates appropriate constraint enforcement preventing administration of drugs with absolute contraindications.

Case 2 (healthy young adult): 30-year-old with normal renal function and no cardiac history. System permitted full multimodal protocol including dexmedetomidine at standard dose (0.5 mcg/kg/hr). At T+11 seconds, simulated

Table 1: Smart NOA Safety Interventions in Representative Patient Profiles

Case	Patient Profile	Initial Protocol	Dynamic Interventions
Case 1: High-Risk Geriatric	78yo, 72kg, ASA-III, eGFR 24 mL/min, Heart Block	**Hard Lockouts:** Dex, Ketorolac blocked. **Permitted:** Lidocaine 1.5 mg/kg/hr, Ketamine 0.2 mg/kg/hr	T+0-15s: Stable hemodynamics (HR 65-75, MAP 70-85). No Dex running due to heart block contraindication. Ketamine/Lidocaine maintained safely.
Case 2: Healthy Young Adult	30yo, 85kg, ASA-II, eGFR 95 mL/min, no comorbidities	**Full Protocol:** Dex 0.5 mcg/kg/hr, Ketamine 0.2 mg/kg/hr, Lidocaine 1.5 mg/kg/hr	T+0-10s: Stable (HR 70-80, MAP 75-90, C_e 0.05-0.08 ng/mL). T+11s: HR=45, C_e=0.12 ng/mL → **BRADYCARDIA & HIGH Ce** → Dex stopped. T+12-20s: HR recovered 55-65, MAP stable → Protocol resumed.

heart rate dropped to 45 bpm coinciding with effect-site concentration reaching 0.12 ng/mL. The concentration-informed interlock triggered immediate dexmedetomidine cessation based on dual criteria (HR < 48 bpm AND C_e > 0.1 ng/mL). Heart rate recovered within 3 seconds, and protocol resumed. This demonstrates the system's ability to distinguish drug-mediated bradycardia (requiring intervention) from transient vital sign fluctuations.

4.2 Protocol Safety Performance

Across all simulated patient scenarios, Smart NOA achieved:

- 100% prevention of contraindicated drug administrations (0 protocol violations)

- 100% appropriate age-based dose adjustments

- Mean detection-to-intervention latency ≤1.0 second

- Zero false-positive interventions during stable hemodynamics with low drug concentrations

The pharmacokinetic modeling component enabled discrimination between drug-mediated and non-drug-mediated hemodynamic changes, a capability absent in conventional vital sign monitoring systems.

4.3 Code Availability and Reproducibility

Complete source code, pharmacokinetic model parameters, simulation scripts, and patient case definitions are publicly available under MIT License at `https://github.com/collingeorge/Smart-NOA-Controller`. The repository includes one-command execution for immediate validation of reported results.

5 Discussion

5.1 Clinical Implications

Smart NOA demonstrates feasibility of deterministic safety supervision enhanced with simplified pharmacokinetic modeling for complex anesthesia protocols. The integration of concentration estimation with hemodynamic monitoring represents a novel approach to closed-loop anesthesia control, bridging the gap between target-controlled infusion systems and rule-based safety supervision.

Three critical innovations distinguish this work from existing approaches. First, hard contraindication enforcement prevents administration errors that typically rely on clinician memory. Second, age-adjusted dosing eliminates mental arithmetic during high-stress induction periods. Third, concentration-informed hemodynamic intervention provides context-aware

safety decisions rather than simple threshold monitoring.

The concentration-informed interlock architecture addresses a fundamental limitation of conventional monitoring: inability to distinguish drug-mediated from non-drug-mediated physiologic changes. A patient experiencing bradycardia from surgical vagal stimulation requires different management than bradycardia from excessive dexmedetomidine effect. Smart NOA's pharmacokinetic model enables this discrimination in real time.

5.2 Patent Strategy and Regulatory Pathway

A U.S. Provisional Patent Application is in preparation (December 2025) claiming the multivariable dynamic interlock architecture with concentration-informed decision logic. Claims focus on the system's integration of pre-administration contraindication enforcement, real-time pharmacokinetic modeling, and physiologic feedback control—not the pharmaceutical agents themselves.

Smart NOA qualifies as Software-as-a-Medical-Device under FDA guidance[6], likely requiring 510(k) clearance as a moderate-risk device. The deterministic architecture facilitates validation through extensive simulation testing and retrospective analysis of de-identified anesthesia records. Prospective clinical trials would compare standard practice against Smart NOA-supervised delivery, measuring protocol adherence, hemodynamic stability, and adverse event rates.

Integration with certified infusion pumps would occur through standardized communication protocols (e.g., IEC 60601-1-8), with Smart NOA functioning as an external supervisory layer rather than modifying pump firmware directly.

5.3 Limitations

This work presents a proof-of-concept with several critical limitations. The pharmacokinetic model employs simplified parameters derived from literature approximations rather than patient-specific covariates. Clinical implementation would require population pharmacokinetic models accounting for age, weight, hepatic function, and genetic polymorphisms affecting drug metabolism[4].

Simulation with synthetic vital signs cannot capture the full complexity of real surgical cases, including rapid physiologic changes, equipment artifacts, or concurrent interventions. The current implementation monitors only two vital signs; clinical deployment would require integration with comprehensive anesthesia monitors.

The concentration threshold of $C_e > 0.1$ ng/mL for intervention represents an initial estimate requiring validation with clinical data correlating dexmedetomidine concentrations to hemodynamic effects. Individual variability in drug sensitivity may necessitate adaptive thresholds based on observed patient responses.

Hard lockouts implement binary contraindication logic, whereas clinical decision-making often involves risk-benefit assessments. Future versions should incorporate tiered warning systems allowing documented clinician override for exceptional circumstances.

5.4 Future Directions

Evolution toward clinical deployment requires three phases. Phase 1 (current work) establishes core architecture and validates logical correctness through simulation. Phase 2 involves retrospective validation using de-identified anesthesia records, testing whether the system would have prevented documented adverse events. Phase 3 requires prospective clinical trials comparing outcomes between standard practice and Smart NOA-supervised cases.

Refinement of pharmacokinetic models using Bayesian estimation techniques could enable patient-specific parameter adaptation based on observed concentration-effect relationships[5]. Integration with continuous drug concentration monitoring (e.g., microdialysis, biosensors) would eliminate reliance on model-based estimates.

Expansion beyond NOA to total intravenous

anesthesia, regional anesthesia adjuncts, and pediatric protocols represents natural extensions. Integration with closed-loop blood pressure control and processed EEG monitoring could enable comprehensive autonomous anesthetic management under human supervision.

The open-source architecture encourages clinical collaboration to refine protocols, validate pharmacokinetic parameters, and extend monitoring capabilities. The MIT License permits commercial derivative works while maintaining a freely available reference implementation.

5.5 Comparison to Existing Systems

Current anesthesia information management systems provide alert generation without autonomous intervention capability. Smart NOA differs fundamentally by executing control authority over drug delivery with pharmacokinetic context.

Existing closed-loop systems (e.g., McSleepy, SEDASYS) utilize PID controllers optimizing single targets based on processed EEG[8]. Smart NOA implements rule-based multi-variable constraints prioritizing safety bounds over optimization, aligning with clinical risk management philosophy. The concentration-informed architecture represents a hybrid approach: model-based concentration estimation with rule-based safety logic.

6 Conclusion

Smart NOA demonstrates that deterministic, concentration-informed safety supervision for opioid-free anesthesia is technically feasible using modest computational resources and transparent rule-based logic enhanced with simplified pharmacokinetic modeling. Integration of effect-site concentration estimation with hemodynamic monitoring enables context-aware safety decisions unavailable in conventional vital sign monitoring.

This work provides an open foundation for clinical validation studies, regulatory approval pathways, and commercial development. We invite collaboration from anesthesiologists, clinical pharmacologists, biomedical engineers, and patient safety researchers to evolve this proof-of-concept into an operating room standard.

The opioid epidemic demands novel approaches to perioperative pain management. Smart NOA offers a path forward where technology augments clinical judgment through concentration-informed decision support, enabling safer adoption of evidence-based opioid-free protocols for vulnerable patient populations.

Data Availability

Source code, pharmacokinetic model implementations, simulation data, and all materials supporting this work are publicly available at `https://github.com/collingeorge/Smart-NOA-Controller` under MIT License.

Competing Interests

The author declares no competing financial interests. A U.S. Provisional Patent Application related to this work is in preparation.

Acknowledgments

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