A simulation-based comparative analysis of PID and LQG control for closed-loop anesthesia delivery

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Abstract: Closed loop anesthesia delivery (CLAD) systems can help anesthesiologists efficiently achieve and maintain desired anesthetic depth over an extended period of time. A typical CLAD system would use an anesthetic marker, calculated from physiological signals, as real-time feedback to adjust anesthetic dosage towards achieving a desired set-point of the marker. Since control strategies for CLAD vary across the systems reported in recent literature, a comparative analysis of common control strategies can be useful. For a nonlinear plant model based on well-established models of compartmental pharmacokinetics and sigmoid-Emax pharmacodynamics, we numerically analyze the set-point tracking performance of three output-feedback linear control strategies: proportional-integral-derivative (PID) control, linear quadratic Gaussian (LQG) control, and an LQG with integral action (ILQG). Specifically, we numerically simulate multiple CLAD sessions for the scenario where the plant model parameters are unavailable for a patient and the controller is designed based on a nominal model and controller gains are held constant throughout a session. Based on the numerical analyses performed here, conditioned on our choice of model and controllers, we infer that in terms of accuracy and bias PID control performs better than ILQG which in turn performs better than LQG. In the case of noisy observations, ILQG can be tuned to provide a smoother infusion rate while achieving comparable steady-state response with respect to PID. The numerical analyses framework and findings, reported here, can help CLAD developers in their choice of control strategies. This paper may also serve as a tutorial paper for teaching control theory for CLAD.

Keywords: Closed-loop control, physiological systems, LQG, PID, integral action, anti-windup, compartmental models, sigmoid-Emax

1. INTRODUCTION

More than 230 million patients undergo major surgeries world-wide under anesthesia (Weiser et al. (2008)). During major surgeries performed under general anesthesia (GA), conventionally, an anesthesiologist would monitor relevant physiological signals that are known to be associated with anesthetic depth, and manually adjust the drug dose. For example, changes in oscillatory patterns in the scalp electroencephalogram (EEG) has been shown to be correlated with behaviorally-defined changes in unconsciousness levels during GA (Purdon et al. (2013)). Such structured drug-dependent changes in the EEG signals have allowed developments of automated EEG-based closed-loop anesthesia delivery (CLAD) systems that can provide precise control of brain states under anesthesia (Bickford (1950); Schwilden et al. (1989); Absalom et al. (2002); Dumont et al. (2009); Shanechi et al. (2013); Puri et al. (2016); Yang et al. (2019)). Analogous systems are also available for blood pressure (BP)-based CLAD (Ngan Kee et al. (2007)).

A typical CLAD system works in a cyclic mode at a fast rate (~ 0.1 s⁻¹) where in each cycle a computer calculates a scalar anesthetic marker from real-time physiological signals (say, EEG or BP) and uses a feedback control strategy to determine the adjustment of drug-dosage for the next cycle. As this iterative procedure continues over time, the anesthetic marker ideally would approach the user-prescribed set-point. The utility of such autopilot systems are in personalized medicine as they can aid anesthesiologists achieve patient-specific precise drug-dosing efficiently, even under resource constrained environments (Dumont and Ansermino (2013); Absalom et al. (2011)).
The CLAD systems reported in prior research, vary with respect to different features, e.g., regime of anesthesia, anesthetic drug, signal modality, marker definition, control strategy, and plant model, just to name a few. For example, the classical output-feedback proportional-integral-derivative (PID) control strategy and its variants have been found to be useful in CLAD applications in human studies (Dumont et al. (2009); Puri et al. (2016); Westover et al. (2015)). The more recent development of using an estimated-state feedback-based optimal control strategy via linear quadratic Gaussian (LQG) regulation have yielded promising results for maintenance of medically-induced coma in animal models (Shanechi et al. (2013)). The success of both PID and LQG, as general control paradigms for CLAD, motivated us to compare them through a numerical experiment in this work.

In this numerical study of CLAD, we consider a specific nonlinear state space model as the plant model. Here the state dynamics, driven by the drug infusion, is described by a four-compartment linear pharmacokinetic (PK) model. The observation dynamics, relating the anesthetic marker and the dynamic state in the effect compartment, is assumed to be described by a sigmoid-Emax pharmacodynamic (PD) model (Meibom and Derendorf (1997)). To generate candidate values of model parameters we use a pair of well-established models in literature for propofol-based PK and corresponding EEG-based PD (Schnider et al. (1998, 1999)). We linearize this nonlinear plant model around a steady-state value and use the resulting linear state space model to determine control parameters. Since LQG is known to have robustness issues (Doyle (1978)) and model-misspecification can lead to steady state errors during set-point tracking, we also consider LQG with an additional integral action (ILQG) on the output error. To address practical constraints, we impose actuator saturation and zero-order holds explicitly. We consider different operating conditions characterized by observation noise and pump-update rates, as well as control parameters. For fixed target trajectory and a given operating condition, we simulate CLAD for multiple subjects to mimic a practical scenario when only a nominal plant model, instead of the true one, is available for controller design. Based on these simulations, we observe PID control leads to faster convergence to setpoint changes relative to LQG and ILQG, but all three provide reasonably similar steady state regulation. In terms of accuracy and bias, PID performs better than ILQG which itself performs better than LQG. In the presence of observation noise, the ILQG can be tuned to provide a smoother infusion rate trajectory while achieving comparable accuracy and bias with respect to the PID.

In the ensuing discussion, Sec. 2 present the core equations for the plant and the control strategies. Sec. 3 presents the details of the numerical simulations, the results and the associated discussion. Finally, Sec. 4 presents the summary of our work.

2. METHODS

2.1 Nonlinear plant model

We model the pharmacokinetics (PK) using a first-order ordinary differential equation as,

\[ \dot{x}(t) = Ax(t) + Bu(t) \]  

where, \( \dot{x} \) indicates \( dx/dt \). Transition matrix, A, and input scaling matrix, B, are prescribed based on a four compartment mammillary model assumption as proposed by Shafer and Gregg (1992), where the effect site is augmented to a three-compartment model as an additional fourth compartment (much smaller in volume relative to the central compartment). The mass of drug in all the compartments at any instant of time, \( t \), is indicated by \( x(t) = [x_1(t), x_2(t), x_3(t), x_4(t)]^T \), \( u(t) \) denotes scalar infusion rate function, \( B = [1, 0, 0, 0]^T \) and transition matrix is given by,

\[
A = \begin{bmatrix}
-k_{10} + k_{12} + k_{13} + k_{14} & k_{21} & k_{31} & k_{41} \\
-k_{12} & -k_{21} & 0 & 0 \\
k_{13} & 0 & -k_{31} & 0 \\
k_{14} & 0 & 0 & -k_{41}
\end{bmatrix}
\]  

Note, that \( u(t) \geq 0 \) and \( x_i(t) \geq 0 \), \( \forall i \in \{1, 2, 3, 4\} \) and \( \forall t \geq 0 \). The PK model described above is illustrated in Fig. 1. We model the pharmacodynamic (PD)\(^4 \) relationship between the a scalar-valued dose-dependent function, say \( y(t) \), of the physiological signal of interest and the effect site amount, \( x_4(t) \), using the following sigmoid-Emax model,

\[
y(t) = E_0 + E_{\text{max}} \frac{(x_4(t)/x_{50})^\gamma}{1 + (x_4(t)/x_{50})^\gamma} \]

where, \( E_0, E_{\text{max}} > 0, x_{50} > 0 \), and \( \gamma > 0 \) are scalar parameters. In the ensuing discussion, the symbol ‘(\( t \))‘, in the notations indicating dynamic variables, will be omitted for brevity. In the computational simulation studies that

![Fig. 1. Schematic of 4-compartment PK model](image)

we perform here, the core plant model taking input \( u(t) \) and generating output \( y(t) \) is given by Eqs. (1) and (3). The nonlinear plant model is characterized by the subject-specific PK-PD parameters \( \Theta_P = \{A, x_{50}, \gamma, E_{\text{max}}, E_0\} \).

2.2 Linear control strategy with output feedback

Steady-state relationships: For linear control design for set-point tracking, we determine relationships among \( y, x \) and \( u \) for a steady state condition. Imposing the steady-state condition, \( \dot{x} = 0 \) in Eq. (1), and denoting the constant values at steady-state as \( y_{ss}, x_{ss} \) and \( u_{ss} \), we obtain

\[
x_{ss} = -A^{-1}Bu_{ss}, \quad (4)
\]

\[
x_{4,ss} = [0, 0, 0, 1]x_{ss}. \quad (5)
\]

\( y_{ss} \) can be calculated by substituting \( x_{4,ss} \) in Eq. (3). When either \( y_{ss} \) or \( u_{ss} \) is specified, one can use the

\(^4\) Conventionally, \( k_{14} \) and \( k_{11} \) are treated as PD parameters (Schnider et al. (1999)), but here, for convenience, we consider them as PK model parameters so as to maintain separate parameter sets for the state and the observation equations.
Linearizing about a steady-state: The relationship between the $y$ and $u$, via Eqs. (1) and (3), is nonlinear. To incorporate a linear feedback control framework to regulate $y$ around a steady-state value, characterized by the tuple $(y_{ss}, x_{ss}, u_{ss})$, we linearize Eq. (3) about this steady-state,

$$ y - y_{ss} = \left( \frac{dy}{dx} \right)_{x_{ss}} (x_{s} - x_{ss}) + \text{higher order terms} $$

Ignoring the higher-order terms, we obtain a new set of equations in terms of dynamic quantities that denote perturbations with respect to respective steady-state values,

$$ \dot{x} = A\tilde{x} + B\tilde{u} $$

$$ y = C\tilde{x} $$

where, $\tilde{y} \equiv y - y_{ss}$, $\tilde{x} \equiv x - x_{ss}$, $\tilde{u} \equiv u - u_{ss}$ and

$$ C = \left( \frac{dy}{dx} \right)_{x_{ss}} = \frac{E_{max}}{x_{50}} \frac{\gamma (x_{ss}/x_{50})^{\gamma - 1}}{(1 + (x_{ss}/x_{50}))^2} $$

**PID control:** To achieve set-point tracking of $y$ about a constant set-point $y_{sp}$, we consider linear system of equations in Eqs. (7) and (8) where linearization is achieved around a user-prescribed state $(y_{o}, x_{o}, u_{o})$. Using PID control gains, $K_p$, $K_I$, and $K_D$, tuned based on this linear system, we implement the following control strategy (Aström and Murray (2010)),

$$ u_{pid} = u_{o} + K_P(y - y_{sp}) + K_I \int (y - y_{sp})dt + K_D \dot{y} $$

where, $y_{sp}$ denotes the user-prescribed setpoint which may or may not be equal to $y_{o}$, but should be in the neighborhood around $y_{o}$ where the linear dynamics regime can still be assumed. The parameter set for the PID is given by $\Theta_{PID} = \{K_P, K_I, K_D, A, x_{50}, \gamma, E_{max}, E_0, u_{o}\}$. This parameter set includes controller gains $(K_P, K_I, K_D)$ as well as the parameters of the nominal linear model that will depend both on the nonlinear plant parameters $(A, x_{50}, \gamma, E_{max}, E_0)$ as well as the state $(u_{o})$ at which the linearization occurs.

**LQG control:** To achieve constant set-point tracking when using LQG strategy, we reformulate the problem in the form of,

$$ \dot{x} = A(x - x_{sp}) + B(u - u_{sp}) + w $$

$$ y - y_{sp} = C_o(x - x_{sp}) + v $$

where, $w$ and $v$ are continuous-time zero-mean Gaussian white noise processes characterized by positive-definite covariance matrix $W$ and positive scalar $V$, respectively (Crassidis and Junkins (2011)). The $C_o$ is determined from Eq. (9) using the linearization state $(y_{o}, x_{o}, u_{o})$ prescribed in terms of either $y_{o}$ or $u_{o}$ (see Sec. 2.2.1). We assume that during a session the controller parameters that depend on $(y_{o}, x_{o}, u_{o})$ will be kept constant, but the set-point $y_{sp}$ may vary around $y_{o}$ in a session. With the problem setup in Eqs. (11) and (12), we can pose the LQG optimal control problem as,

$$ J = \int_0^\infty (x - x_{sp})^T Q (x - x_{sp}) + (u - u_{sp})^T R (u - u_{sp}) dt + \text{higher order terms} $$

such that Eq. (11) holds at every time-point, and $E[\cdot]$ indicates an expectation operation. Assuming the system $(A, B)$ is stabilizable and $(A, C_o)$ is detectable and matrices $Q$ and $R$ are positive semi-definite and positive definite, respectively, the solution of the aforementioned optimal control problem leads to a steady state linear quadratic regulator with control action $u_{lqg}$ given by,

$$ u_{lqg} = u_{sp} - K_L(x - x_{sp}) $$

where, $\tilde{x}$ is the output of a steady-state Kalman filter,

$$ \dot{x} = (A - K_E C_o)(x - x_{sp}) + B(u - u_{sp}) + K_E(y - y_{sp}) $$

Controller gain matrix $K_C$ depends on $A, B, Q$ and $R$. Estimator gain matrix $K_E$ depends on $A, C_o, W$ and $V$. The formulae to calculate $K_C$ and $K_E$ can be found in literature (Athans (1971); Crassidis and Junkins (2011)). The parameter set for the PID is given by $\Theta_{LQG} = \{Q, R, W, V, A, x_{50}, \gamma, E_{max}, E_0, u_{o}\}$. Since we are interested in how the LQG performance changes with regard to the current CLAD problem in the presence and absence of an integral action, we explicitly specify $K_I$. This is in the same spirit as the LQG controller designs that can be simulated using the `lqgtrack` function in Matlab. However, one can also design $K_I$ implicitly within the LQG framework (Grumble (1979)).

**Additional constraints for CLAD simulation:** In the context of CLAD, practical considerations require $u \geq u_{min} = 0$ and $u \leq u_{max}$; the latter constraint can be due to constraints on the physiological system and/or the mechanical actuation system. To mimic this in our simulation, we allow output of the controller, say $u_c$, (such that $c \in \{\text{pid, lqg, ilqg}\}$), goes through a saturation block prescribed as,

$$ u = u_{c} $$

if $0 < u_{c} < u_{max}$,

$$ u = 0 $$

if $u_{c} \leq 0$,

$$ u = u_{max} $$

if $u_{c} \geq u_{max}$.

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![Fig. 2. Schematic block diagram of CLAD simulation setup](image-url)
mechanical phenomenon which can have a short transient before the infusion rate stabilizes around the desired flow rate. To simulate this condition without modeling the drug delivery dynamics explicitly we impose a zero-order hold (zoh) condition on $u$, such that the flow rate $u$ is updated at an interval $T_u$, and held constant until the next update. A similar zoh condition is applied on the output side assuming that it is sampled at rate $T_y$ which may or may not be equal to $T_u$. To mimic the noise in the observations, we also add Gaussian white noise with variance $\sigma^2$ and sampled at every interval $T_y$, to the observation. If $T_y = T_u$ holds, then one can alternatively choose to model plant and controller dynamics in discrete-time governed by incremental dynamic equations. However, this would require the increment time-interval to enter the system matrices that are used to calculate controller gains. Furthermore, modeling the plant in continuous time is conceptually closer to the physiological phenomena governing the true PK-PD phenomena. Therefore, in this work, we try to keep the plant and control blocks independent of any prescribed time-interval, but add the aforementioned constraints, via user-prescribed values of $u_{\text{max}}$, $T_u$ and $T_y$ externally in the complete simulation block diagram (Fig. 2).

![Fig. 1](image1.png)

Table 1. Performance metrics for PID (Fig.3(a-d)), LQG with $\rho = 10^{-13}$ (Fig.4(a-d)), ILQG with $\rho = 10^{-6}$ (Fig.4(e-h)), ILQG with $K_I = 10, \rho = 10^{-13}$ (Fig.5(a-h)) and corresponding EEG-based pharmacodynamics (Schneider et al., 1999, Table 3), where for the latter we use only the age-adjusted parameters for the ascending sigmoidal function in the bi-phasic response.
are: these features. The parameters, for this nominal patient

\[ \begin{align*}
0 \text{ weight} & = 79 \\
10 \text{ years} & = 35 \\
5 \text{ cm} & = 177.5 \\
50 \text{ kg} & = 79.5 \\
\end{align*} \]

LQG-based CLAD with two control designs \( \rho \text{ based CLAD} \): a PID-based CLAD (Fig. 3(a-d)), an ILQG-following subsection. For each combination of \( (T_u, V) \), we simulate: a PID-based CLAD (Fig. 3(a-d)) and an LQG-based CLAD simulation under same conditions, but with \( K_I = 0 \) (Fig. 4(a-d) and Fig. 4(e-h)). For each of these operating conditions, we simulate CLAD sessions for \( N_p \) subjects such that the nominal plant, \( \Theta \text{nom} \), is characterized by a respective \( \Theta_p \text{nom} \). To calculate the \( \Theta_p \text{nom} \), we consider a nominal subject (age = 35 years, height = 177.5 cm, weight = 79.5 kg, male) using the median of each of these features. The parameters, for this nominal patient are: \( k_{10} = 0.4282 \text{ min}^{-1} \), \( k_{12} = 0.4005 \text{ min}^{-1} \), \( k_{13} = 0.1958 \text{ min}^{-1} \), \( k_{31} = 0.0664 \text{ min}^{-1} \), \( k_{31} = 0.0035 \text{ min}^{-1} \), \( k_{41} = 0.4560 \text{ min}^{-1} \), \( x_{50} = 6.8 \times 10^{-5} \text{ mg} \), \( \gamma = 3.0965 \). All simulations are performed using Matlab/Simulink. To assess the performance across controller designs and across multiple simulation conditions, we use the following inaccuracy and bias metrics (Dumont et al. (2009)):

\[
\begin{align*}
\text{Inaccuracy}, \epsilon_I & = \text{median} \{100[|y_k - y_{sp}|]/y_{sp}\} \quad (20) \\
\text{Bias}, \epsilon_B & = \text{median} \{100(y_k - y_{sp})/y_{sp}\} \quad (21)
\end{align*}
\]

where, \( y_k \) refers to observation at the \( k \)-th time-point. We also keep track of average infusion rate \( u_{avg} \) throughout the entire session.

3.2 CLAD simulations

For each control strategy we simulate for every patient set-point tracking with \( T_u \in \{5/60 \text{ min}, 10/60 \text{ min}\} \), and \( V = \{10^{-6}, 10^{-4}\} \) under conditions described in the following subsection. For each combination of \( (T_u, V) \), we simulate: a PID-based CLAD (Fig. 3(a-d)), an ILQG-based CLAD with two control designs \( \rho = 10^{-3}, K_I = 0 \) (Fig. 5(a-d)) and \( \rho = 10^{-6}, K_I = 1 \) (Fig. 5(e-h)), and an LQG-based CLAD simulation under same conditions, but with \( K_I = 0 \) (Fig. 4(a-d) and Fig. 4(e-h)). For each of these operating conditions, we simulate CLAD sessions for \( N_p \) subjects such that the nominal plant and true plant are different. In these simulations, every subject is characterized by a respective \( \Theta_p \) value, whereas controller parameters are characterized by a fixed set of parameters \( \Theta_C \) determined based on a nominal model of the plant, \( \Theta_{Pnom} \). To calculate the \( \Theta_{Pnom} \), we consider a nominal subject (age = 35.5 years, height = 177.5 cm, weight = 79.5 kg, male) using the median of each of these features. The parameters, for this nominal patient are: \( k_{10} = 0.4282 \text{ min}^{-1} \), \( k_{12} = 0.4005 \text{ min}^{-1} \), \( k_{13} = 0.1958 \text{ min}^{-1} \), \( k_{31} = 0.0664 \text{ min}^{-1} \), \( k_{31} = 0.0035 \text{ min}^{-1} \), \( k_{41} = 0.4560 \text{ min}^{-1} \), \( x_{50} = 6.8 \times 10^{-5} \text{ mg} \), \( \gamma = 3.0965 \). All simulations are performed using Matlab/Simulink. To assess the performance across controller designs and across multiple simulation conditions, we use the following inaccuracy and bias metrics (Dumont et al. (2009)):

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\end{align*}
\]

where, \( y_k \) refers to observation at the \( k \)-th time-point. We also keep track of average infusion rate \( u_{avg} \) throughout the entire session.

3.3 Discussion

Our final assessment of controller performance based on the simulated CLAD sessions, is based on both the numerical outputs of \( \epsilon_I, \epsilon_B, u_{avg} \) (Table 1) and visual inspection of output and control trajectory plots (Figs. 3, 4, 5). The inaccuracy and bias metrics for the PID is found to be lower than both ILQG and LQG. The integral action applied within the ILQG framework indeed improves on the LQG, e.g. compare Fig. 4(a-d) vs. Fig. 5(a-d) and Fig. 4(e-h) vs. Fig. 5(e-h). All 3 control strategies show stable performance under the values of \( (T_u, V) \) considered here. Also, from visual inspection we can infer that PID is able converge to set-point faster than LQG or ILQG, but all of them are able to provide stable regulation once output converges to the set-point. Comparing Figs. 3(a-d), 5(a-d), and 5(e-f), show that by lowering \( \rho \) (the relative weighting of state cost to input cost in the LQG quadratic objective function) we can tune the ILQG to achieve a control signal that is not as sensitive to the input noise and leads to acceptable steady-state performance. In the all the simulations except for Fig. 4(e-h), the average control effort, \( u_{avg} \), is found to be almost similar across all the control strategies. Also, comparing Fig. 4(a-b) and Fig. 4(e-h), we infer that if LQG without integral action is to be used, then it is preferable to set a high value of \( \rho \).
4. CONCLUSION

In this work, we compared three control strategies: PID, LQG, and ILQG for a CLAD application. For the CLAD problem considered here (set-point tracking of output from a single-input single-output PK-PD system described by Eqs. (1) and (3)), we draw the following inference from our analyses: PID can help with faster convergence to setpoint that can occur due to first activation of closed-loop mode and set-point changes. Once set-point is achieved PID, ILQG and LQG can provide stable set-point tracking. LQG requires a very high penalty on state cost relative to actuation cost (in Eq. (14)) to provide acceptable setpoint tracking performance, but adding an integral action via an ILQG can lead to acceptable tracking performance with lower relative cost. In the presence of observation noise, ILQG can be tuned to achieve temporally smoother actuation with acceptable set-point tracking performance relative to a PID controller.

We envisage that this work will be useful to guide controller choices in future CLAD designs, and numerically assessing their performance prior to implementing in human or animal subjects. Since the framework involving compartmental PK and sigmoid-Emax PD models considered in this study is quite general (Meibohm and Derendorf (1997)), our work can be relevant to CLAD applications beyond the specific anesthetic drug and physiologic signal definitions of the assumed PK-PD model (Schnider et al., 1998, 1999)). Furthermore, this paper may also serve as a tutorial introduction to applications of control theory in CLAD systems.

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