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Analysis and Preliminary Results of a Feedback-Feedforward Controller for Depth of Anesthesia

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Abstract: In a computer-based anaesthesia control system, the depth of hypnosis must be correctly maintained. The regulated variable is the Bispectral Index scale (BIS) controlled via the Propofol drug rate. The anesthesiologist administers Propofol to prevent unwanted fluctuations in the controlled variable during surgical stimulation, which acts as an unmeasurable disturbance on the BIS signal. In this paper, a feedback controller is paired with a feedforward control action. Based on existing clinical protocols, a digitalized disturbance signal that mimics the actual surgical stimulus is employed in the feedforward controller design as a measurable disturbance. To account for the time delay in the BIS measurements, a time delay estimation algorithm is developed and used to estimate the patient time delay. The digitalized disturbance signal is then shifted based on the estimated time delay to ensure a pre-emptive action of the feedforward controller. Two different designs of the feedforward controller are developed. Closed loop simulations considering a nominal patient with and without the feedforward control action are presented and compared. The results show that the surgical stimulus is better tackled using a feedforward control action, even if the actual surgical stimulus is not entirely known.

Keywords: feedforward control, fractional order control, depth of hypnosis, time delay estimation, closed loop control of anesthesia.

1. INTRODUCTION

Historically speaking, the dosing of drugs used in general anaesthesia is largely based on trial and error and on the experience of the anesthesiologists. One major challenge for anaesthesia automation is replicating this experience. Clearly, this necessitates the use of feedforward information derived from measurable signals associated with disturbances (Nunes et al., 2009). One of the most researched parts of anesthesia refers to the control of the depth of hypnosis. In this case, the Bispectral Index (BIS) has been deemed as suitable for an accurate estimation of the level of unconsciousness (Soltesz et al., 2020). Dedicated sensors exist to measure the BIS signal, which has facilitated research on the possibilities of using automatic control to replace or at least aid the anesthesiologist. The BIS signal is 100 for a fully awake patient and decreases towards 0, a state of no cortical activity, due to the administration of Propofol. In most clinical interventions, a BIS signal of 50 is considered suitable for surgery, but the actual value can vary in a range from 40 to 60 (Rosow and Manber, 2001).

Several control strategies based on feedback measurements of the BIS signal have been proposed (Merigo et al., 2019), (van Heudsen et al., 2018), (Schiavo et al., 2023), (Padula et al. 2016), to name just a few. In some cases, researchers have proposed separate controllers to tackle the induction and the maintenance phases (Hegedus et al., 2022). One of the key issues is the sluggish response of the controller in the induction phase (Schiavo et al., 2021), when the BIS signal should drop to 50 in less than 5 minutes. Solutions to this issue have been proposed by combining the feedback controller with a minimum-time feedforward action. This is responsible for providing a personalized Propofol bolus during the induction phase, which is calculated using a nominal patient model (Schiavo et al., 2021). The feedforward action practically mimics the anesthesiologist.

Previous research has also shown that using feedback control combined with information from other measurable signals, such as other drugs supplied to the patient or the electromyography EMG signal can significantly improve the closed loop performance (Nunes et al., 2009). For example, the EMG influences surface EEG and thus BIS calculation. Surgical stimulus triggers a higher level of EMG (Wheeler et al., 2005). From a control engineering perspective, the measured EMG level can be used as a measurable disturbance or at least offer some information related to the surgical stimulus (Nunes et al., 2009).

Whenever measuring the disturbances is possible, a feedforward control strategy represents an efficient way to counteract their effect. However, in anesthesia, measuring the surgical stimulus is close to impossible. But, in most common and uncomplicated surgical procedures the surgeons and anaesthesiologists follow a sequence of steps that is fixed and abide by a predefined protocol. These are commonly occurring in a prescribed manner and usually last for a predefined period. This information can be used to produce a digitalized surgical stimulus, stored in a computer alongside the feedback control algorithm. This digitalized surgical stimulus can be employed in a feedforward control strategy, as a substitute of the actual unmeasurable surgical stimulus. The digitalized surgical stimulus replaces the measurable disturbance in a standard feedforward control strategy.

In this paper, a preliminary solution that combines feedback-feedforward (FB-FF) control is proposed, where a digitalized signal is used to mimic the surgical stimulus. To account for the time delays that affect the BIS signal, a time delay estimation algorithm is also developed with the estimation performed during induction. The digitalized disturbance signal is triggered by the onset of the Propofol initial dose during induction. Considering a mean period of time for the BIS signal to reach 50 the digitalized disturbance signal is shifted with the estimated time delay to anticipate the surgical stimulus. A robustness analysis regarding variations in the amplitude and occurrence of the actual surgical stimulus compared to its digitalized version is performed. The simulation results show that the proposed solution leads to better closed loop results compared to the feedback only approach, even when amplitude and time delay variations are present.

The paper is structured as follows. Section 2 presents the design of the feedback-feedforward controller with time delay estimation and digitalized surgical stimulus. Simulation results, including the robustness analysis, are included in Section 3, while the concluding remarks are included in Section 4.

2. DESIGN OF FEEBACK-FEEDFORWARD CONTROLLERS

2.1 Surgical stimuli

To test the efficiency of the designed control algorithms in keeping the BIS values in a predefined range during maintenance, a commonly used surgical stimulus (Ionescu et al., 2021), (Hegedus et al., 2023) has been used. A nociceptor stimulation occurs whenever a surgical stimulus occurs (Ionescu et al., 2024). To simulate nociception, a simplified mathematical model has been previously proposed (Ionescu et al., 2021):

$$\mathrm{NOCI}(s) = \frac{k(s^2+z_1s+z_2)(s^2+z_3s+z_4)(s^2+z_5s+z_6)}{(s^2+p_1s+p_2)(s^2+p_3s+p_4)(s^2+p_5s+p_6)} \quad (1)$$

The surgical stimulus affects the BIS signal and acts as a disturbance that is filtered through the nociception model in (1).

Here, a different surgical stimulus compared to (Hegedus et al., 2022) is used to analyse the effect of using a feedforward action combined with the standard feedback controller. The surgical stimulus signal is indicated in Fig. 1 and corresponds to a series of events occurring in this order: intubation; incision; followed by a period of low excitation; various surgical procedures including abrupt stimuli, as well as larger stimulation period represented as a series of surgical events with various amplitudes and period; and withdrawal of stimulation during the closing period. Most of the times, for a nominal patient without complications, the same steps are performed, which allows for a digitalization of the surgical stimulus as indicated in Fig. 1 (blue line). This can be easily implemented on a computer using arrays in Matlab. Several variations in the amplitudes of the nominal digitalized surgical stimulus are represented in the same figure with dotted lines.

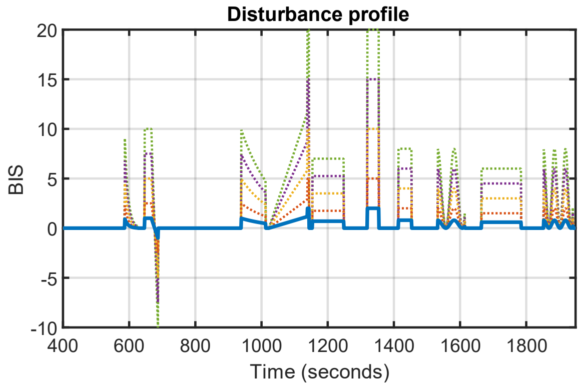

Fig. 1. Digitalized surgical stimulus (nominal signal in blue, amplitude variations in dotted lines)

Feedback control algorithms have been designed and tested in terms of their efficiency in rejecting surgical stimulus effect. In the next section, such a feedback controller is compared with a feedback-feedforward approach. Various case scenarios regarding feedback-feedforward control are analysed as indicated hereafter:

- Only feedback control and no feedforward action
- Feedback + feedforward control with amplitude variations and uncertainties
- Feedback + feedforward control with time delay variations and precise estimation

In both cases of the FB-FF approach, a transient design and a steady state design of the feedforward controller are tested and compared. A robustness analysis is also performed by considering variations of the actual surgical stimulus, compared to its digitalized version, both in amplitude and occurrence. Since the depth of hypnosis is affected by dead-time, a preliminary FB-FF control approach with time delay estimation is proposed and presented in subsection 2.4.

2.2 The feedback controller

The induction phase of anesthesia corresponds to the patient receiving initial Propofol doses to reach a depth of hypnosis accurate for surgery, i.e. BIS=50. In this paper, the focus lies on the way the surgical stimulus is treated by the proposed control algorithms. Hence, only the maintenance phase is analysed. The BIS signal should be kept within 40-60, with a fast rejection of output or input disturbances (surgical stimuli or anaesthesiologist boluses). Several fractional order controllers have been designed and evaluated (Hegedus et al., 2022) in terms of the following performance criteria:

- Time-to-Target (TT) defined as the maximum required time for the BIS level to be brought back in the range [45-55].
- BIS-APEX, BIS-NADIR defined as the largest/smallest amplitude of the BIS signal (it should not increase more than 60 or decrease below 40).
- Integral of Absolute Error (IAE) defined as: $\min(\mathrm{IAE})$, $\mathrm{IAE}=\int_0^\infty |e(t)|dt$, with the error signal computed as $e(t)=50-\mathrm{BIS}(t)$.
- Constraints on the sensitivity and complementary sensitivity functions.

The controller that achieved the best closed loop performance, as well as its tuning are given in (Hegedus et al., 2022):

$$H_{FOPI}(s) = 0.0053\left(1 + \frac{0.0532}{s^{1.04}}\right) \tag{2}$$

2.3 Feedforward controller design

A simplified feedforward controller design is proposed here. The block diagram of the feedback-feedforward control strategy is given in Fig. 2, where NOCI(s) stands for the nociception as indicated in (1) and $C_D(s)$ is the feedforward controller. In this manuscript, we assume that the surgeon obeys a standard surgical routine and that the digitalized surgical stimulus is identically to the actual surgical stimulus. In practice, however, the two can differ in amplitude, duration and occurrence. The control diagram in Fig. 2 is designed to indicate this situation, where a digitalized surgical stimulus based on a standard protocol is supplied to the $C_D(s)$ controller and used to trigger a control action through the feedforward controller, computed as:

$$C_D(s) = \frac{\mathrm{NOCI(s)}}{\widetilde{H}_{DOH}(s)} \tag{3}$$

where $\widetilde{H}_{DOH}(s)$ is the delay free part of $H_{DOH}(s) = \frac{\mathrm{BIS(s)}}{\mathrm{PROP}(s)} e^{-\tau_m s}$ - the transfer function that describes the depth of hypnosis as a ration between the output signal BIS(s) and the input signal, PROP(s) – the administered Propofol. Previous research has also shown that a dead time τ_m occurs for the BIS signal whenever Propofol is administered (Ionescu et al., 2021). A surgical stimulus, however, has an immediate effect on the BIS signal. From a control engineering point of view, since the process dead-time is larger than that of the estimated disturbance, perfect disturbance rejection is not possible (Hast and Hagglung, 2014). The feedforward controller in (3) is improper and cannot be implemented in practice. In this manuscript, an approximate feedforward controller is used instead of the one in (3):

$$C_D(s) = \frac{\mathrm{NOCI(s)}}{\widetilde{H}_{DOH}(s)(T_f s+1)} \tag{4}$$

where T_f is the time constant of the disturbance filter added to make the feedforward controller in (4) proper. Usually, the T_f is taken to be at least two times smaller than the smallest time constant in the $C_D(s)$ controller. A simplified approach to the design of the feedforward controller in (4) consists in the steady state approximation of (4) as given next:

$$C_D(s) = \frac{\mathrm{NOCI(0)}}{\widetilde{H}_{DOH}(0)} \tag{5}$$

where the steady state values of NOCI(s) and the patient model $H_{BIS}(s)$ have been considered. Disturbances are due to surgical stimuli occurring during maintenance phase when both Propofol and BIS are constant. Thus, the steady state approach in (5) is more feasible from a clinical point of view.

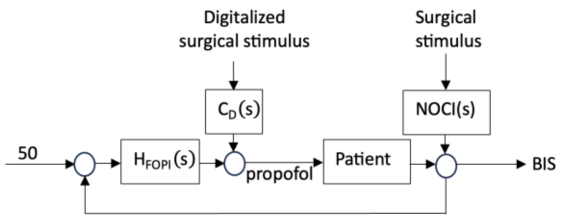

Fig. 2. Feedback-feedforward control strategy for depth of anesthesia

2.4 Feedforward controller design with time delay estimation and disturbance trigger

Previous research has also shown that the dead-time τ_m is affected by patient variability, ranging from 20 seconds to more than 2 minutes (Mihai et al., 2024). A simple time delay estimation algorithm is implemented to enable a better performance of the feedforward control loop. The estimation is performed prior to the beginning of the surgery, during the induction phase. The time delay estimation algorithm is given in Fig. 3 and its accuracy has been tested for a randomized set of 22 patient models, with great variability in the dead-time.

Delay estimation algorithm

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1: Take the initial value from the BIS vector. Denote it with: init_bis
2: Establish a threshold of 10% from the initial value. Denote it: Th1
3: Establish a threshold of 1% - 2% from the initial value. Denote it: Th2
4: for i = 3 to n do
5:     Find i for which init_bis – BIS(i) > Th1
6:     for j = 0 to (i-1) do
7:         Find j for which init_bis – BIS(i-j) < Th2
           Denote est_delay = t(i-j-1)
           break the loop
8: delay = est_delay
```

Fig. 3. Time delay estimation algorithm

The algorithm in Fig. 3 has been designed with a sampling period of T_s=5 seconds, which can be adjusted. It has an accuracy of 86.7% in estimating the time delay with an error of 1 sample and 63.6% in estimating the time delay with a maximum of 3 samples.

The feedback-feedforward control structure in Fig. 2 is altered to include the time delay estimation algorithm. The proposed control structure is given in Fig. 4. The estimated dead-time is used to update and shift the digitalized disturbance signal. Hence, the feedforward controller is enabled to take pre-emptive action τ_m seconds before the actual surgical stimulus occurs.

3. SIMULATION RESULTS

The nominal patient in the benchmark model developed in (Ionescu et al., 2021) is used to analyse the performance of the feedback-feedforward control approach, presented in Section 2. The PK-PD model of this patient is described in detail in (Ionescu et al., 2021). To design the $C_D(s)$ controller, a simplified model for the depth of hypnosis is used determined based on the patient model available in (Ionescu et al., 2021):

$$H_{DOH}(s) = \frac{-16.64(s+0.024)}{(s+0.18)(s+0.021)} e^{-19.7s} \tag{6}$$

Then, the model-based feedforward controller in (4) is computed as:

$$C_D(s) = \frac{\mathrm{NOCI}(s)(s+0.18)(s+0.021)}{-16.64(s+0.024)(0.01s+1)} \tag{7}$$

The corresponding steady state feedforward controller is given by:

$$C_D(s) = \frac{\mathrm{NOCI}(0)}{\tilde{H}_{DOH}(0)} = -105.65 \tag{5}$$

The two feedforward controllers are implemented in the block diagram of Fig. 4, where the feedback controller is in both cases the one in (2).

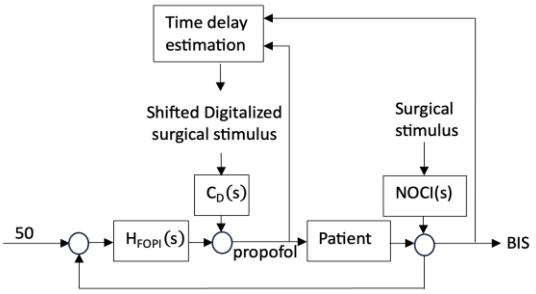


Fig. 4. Feedback-feedforward control strategy with time delay estimation for depth of anesthesia

3.1 Analysis of disturbance magnitude rejection

The first aspect to be considered in assessing the robustness of both the steady state and model-based feedforward controllers pertains to their ability to reject the disturbances of varying magnitudes. The analysis consists of varying the disturbance profile magnitude as indicated by the dotted lines in Fig. 1, while considering precise time delay estimation. Table 1 contains the results, where the gain of the digitalized surgical stimulus in Fig. 1 has been varied up to 10 times (indicated as 10x in Table 1). The corresponding maximum amplitudes of the resulting digitalized surgical stimulus are also indicated in Table 1. The model-based feedback-feedforward (FB-FF) controller exhibits notable resilience against larger disturbances when compared to the steady state variant, yielding superior results by a margin of 40-80% considering the overall performance indices (IAE, ISE).

Table 1. Disturbance rejection comparison of steady state and model-based feedforward controllers

FB-FF Steady state					
(Gain, Max. amplitude)	TT (s)	BIS-APEX	BIS-NADIR	IAE (10^1)	ISE (10^2)
1.0x, 2	0	51.83	47.86	40.83	1.92
2.5x, 5	0.29	54.69	44.84	64.98	6.40
5.0x, 10	6.49	59.45	40.12	110.66	22.72
7.5x, 15	20.16	64.21	35.81	159.62	50.88
10x, 20	22.21	68.97	31.94	211.14	92.14
FB-FF Model Based					
(Gain, Max. amplitude)	TT (s)	BIS-APEX	BIS-NADIR	IAE (10^1)	ISE (10^2)
1.0x, 2	0	50.45	49.29	32.84	1.16
2.5x, 5	0	51.22	48.65	38.65	1.59
5.0x, 10	0	52.37	47.75	52.30	3.40
7.5x, 15	0	53.50	43.92	70.64	7.73
10x, 20	2.31	55.18	39.63	98.36	18.25

3.2 Analysis of disturbance magnitude uncertainties

To highlight the worst-case scenario for measurement errors, the analysis now employs the largest disturbance magnitude (10x, maximum 20). For minor disturbances (magnitudes below 5), there was no substantial variance in the inaccurate measurement of the disturbance magnitude. Similarly, the inaccurately estimated time delay did not exert a significant impact on the response. This is due to the disturbance magnitude itself and due to the feedback component managing the incorrect signal of the feedforward component.

The subsequent analysis in Table 2 examines the wide range of poorly measured disturbance magnitudes, with negative signs denoting undermeasurement and positive signs indicating overmeasurement. Fig. 5 a) graphically represents the corresponding digitalized surgical stimuli.

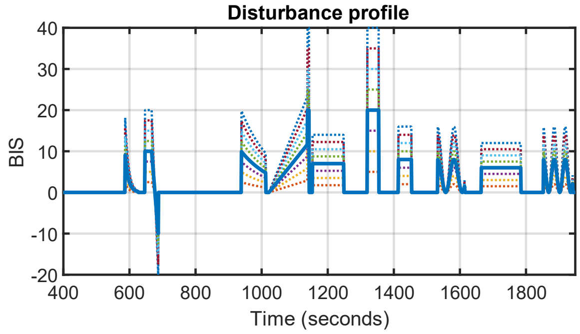
Table 2. Disturbance magnitude uncertainty comparison of steady state and model-based feedforward controllers

FB-FF Steady state					
Measurement	TT (s)	BIS-APEX	BIS-NADIR	IAE (10^1)	ISE (10^2)
-75%	37.69	69.40	34.88	396.98	256.66
-50%	34.17	69.26	35.10	320.64	179.97
-25%	24.84	69.12	33.52	254.34	125.64
100%	22.21	68.97	31.94	211.14	92.14
+25%	20.78	68.81	30.37	195.74	77.91
+50%	16.53	68.65	28.82	218.16	81.41
+75%	14.17	68.48	27.31	263.45	101.16
FB-FF Model					
Measurement	TT (s)	BIS-APEX	BIS-NADIR	IAE (10^1)	ISE (10^2)
-75%	38.03	65.50	36.67	373.92	215.59
-50%	34.16	61.76	39.79	273.08	113.23
-25%	24.69	58.32	41.50	176.55	49.11
100%	2.31	55.18	39.63	98.36	18.25
+25%	3.07	55.87	37.67	100.03	16.85
+50%	5.44	60.33	35.68	172.05	41.19
+75%	9.38	64.73	33.69	256.13	87.92

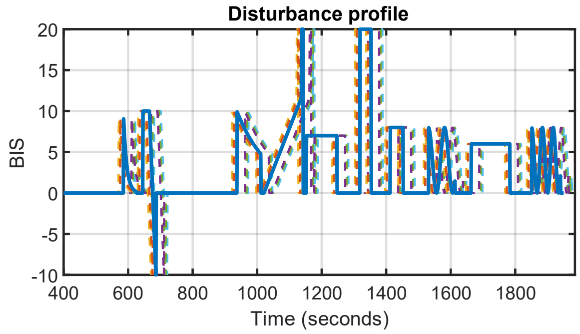
The model-based variant consistently outperforms the steady state. Substantial undermeasurements (below 25%) significantly diminish the feedforward contribution, while overmeasurements lead to a more aggressive response, reducing time-to-target (TT) until 75% overmeasurement. However, the performance indices gradually deteriorate in this scenario.

3.3 Analysis of time delay uncertainties

Time delay uncertainties may arise from imprecise estimates of the patient's time delay or deviations from the surgery protocol timings by the surgeon, causing shifts in disturbance occurrences. The investigation considered a scenario with precise magnitude measurement, using the maximum magnitude as previously specified (10x, maximum 20). The time delay of disturbance occurrences was systematically varied, as indicated in Fig. 5b). Ideally, the estimated time delay should align with the patient's time delay (19.7s). Instances occurring before this point denote errors in patient time delay estimation, while those occurring afterward indicate errors in either patient time delay estimation or surgery protocol time shifting.



a)



b)

Fig. 5. Digitalized disturbance profiles considering a mismatch with the actual surgical stimulus in the a) magnitude b) occurrence (time delay)

A comparison of the performance of the proposed feedback-feedforward controllers considering a mismatch between the occurrence of the digitalized surgical stimulus and that of the actual surgical stimulus is indicated in Table 3. The results in Table 3 highlight a notable decline in the feedback-feedforward control strategy's performance due to both patient time delay estimation errors and deviations in surgery protocol timings. This highlights the critical importance of accurate patient time delay estimation, while emphasizing the necessity of addressing surgery protocol delays, which are more prone to occurrence and carry crucial importance.

Considering the overall performance indices (IAE, ISE) in Table 3, the results show that up to an error of 15s, the feedforward controllers outperform in certain aspects the feedback-only controller outlined in Table 4. Notably, the model-based variant is more sensitive to time delay errors due to its dynamics.

3.4 Comparison of Feedback and Feedback-Feedforward control

The optimal outcomes of the steady-state and model-based feedforward strategies are ultimately showcased in contrast to the Feedback-only strategy in Table 4, with the corresponding responses depicted in Fig. 6. Under precise timing and accurate disturbance measurement, the feedforward strategy surpasses traditional feedback-only control. However, real-world scenarios involve combinations of magnitude measurement errors and time delay estimation errors, necessitating a more comprehensive examination of these factors in future studies.

Table 3. Comparison of disturbance time delay estimation uncertainties

FB-FF Steady state					
Estimated cumulative delay (s)	TT (s)	BIS-APEX	BIS-NADIR	IAE (10^1)	ISE (10^2)
10	25.53	70.47	28.41	410.59	314.15
15	23.19	70.38	29.67	311.71	201.82
19.7	22.21	68.97	31.94	211.14	92.14
25	27.32	63.19	38.65	183.87	60.56
30	42.73	66.46	36.85	268.60	124.79
35	48.32	68.42	35.96	367.60	221.34
FB-FF Model					
Estimated cumulative delay (s)	TT (s)	BIS-APEX	BIS-NADIR	IAE (10^1)	ISE (10^2)
10	23.02	70.21	29.12	332.26	245.91
15	21.10	70.12	30.54	207.00	124.48
19.7	2.31	55.18	39.63	98.36	18.25
25	17.60	68.30	29.97	253.43	140.96
30	23.73	70.82	29.91	386.78	276.40
35	28.71	74.50	29.86	491.80	407.33

Table 4. Comparison of feedback and optimal feedback-feedforward control strategies

Control strategy	TT (s)	BIS-APEX	BIS-NADIR	IAE (10^1)	ISE (10^2)
Feedback only control	41.94	69.95	32.97	477.31	357.10
Steady state FB-FF control	22.21	68.97	31.94	211.14	92.14
Model-based FB-FF control	2.31	55.18	39.63	98.36	18.25

4. CONCLUSIONS

The depth of hypnosis must be correctly maintained in a computer-based anaesthesia control system. Propofol is administered by the anesthesiologist to prevent unwanted fluctuations in the patient's BIS signal during surgical stimulation, which act as an unmeasurable disturbance. In this paper, a feedback-feedforward controller is developed. Based on existing clinical protocols, a digitalized disturbance signal that mimics the actual surgical stimulus is used as a measurable disturbance in the feedforward controller design. The patient time delay is assessed online using a dedicated estimation algorithm. The digitalized disturbance signal is then shifted based on the estimated time delay to ensure that the feedforward controller acts pre-emptively. The feedforward controller is designed in two different ways. Closed loop simulations with and without the feedforward control action are presented and compared for a nominal patient. The findings show that using a feedforward control action to manage the surgical stimulus is more effective, even when the exact details of the stimuli are unknown. Nonetheless, maintaining precise timing is critical for maintaining performance gains.

Further research includes the extension of the proposed control design to situations where the BIS time delay is variable, as well as an analysis of the proposed method on other patients.

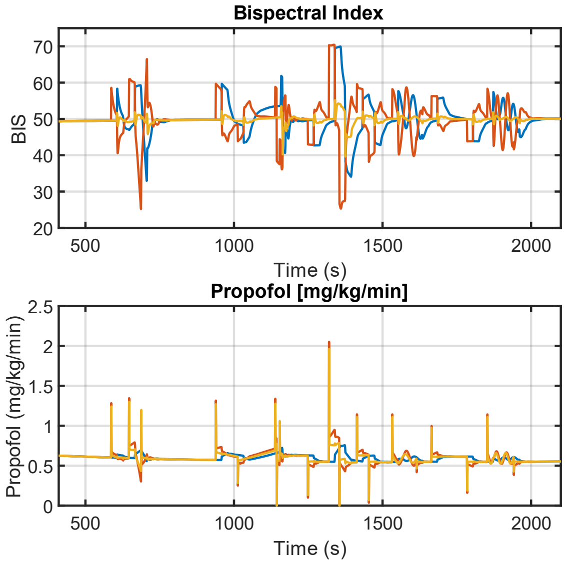


Fig. 6. Comparison between FB-Only control (blue), Optimal Steady state FB-FF control (red) and Optimal model-based FB-FF control (yellow)

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REFERENCES

Ionescu, C.M., Neckebroek, M., Ghita, M., Copot, D. (2021). An Open Source Patient Simulator for Design and Evaluation of Computer Based Multiple Drug Dosing Control for Anesthetic and Hemodynamic Variables, *IEEE Access*, vol. 9, pp. 8680-8694.

Ionescu, C.M., Copot, D., Yumuk, E., De Keyser, R., Muresan, C.I., Birs, I.R., Ben Othman, G., Farbakhsh, H., Ynineb, A.R., Neckebroek, M. (2024). Development, Validation, and Comparison of a Novel Nociception/Anti-Nociception Monitor against Two Commercial Monitors in General Anesthesia, *Sensors*, vol. 24, paper 2031.

Rosow, C., Manberg, P.J. (2001). Bispectral index monitoring, *Anesthesiol. Clin. N. Am.*, vol. 19 (4), 947–966.

Hegedus, E., Ghita, M., Birs, I. R. , Copot, D., Muresan, C.I. (2023). Robustness analysis of a fractional order control system for the hemodynamic variables in anesthetized patients, *2023 European Control Conference*, pp. 1-6

Padula, F., Ionescu, C., Latronico, N., Paltenghi, M., Visioli, A., Vivacqua, G. (2016), Inversion-based propofol dosing for intravenous induction of hypnosis, *Commun. Nonlinear Sci. Numer. Simul.*, vol. 39, pp. 481–494.

Hast, M., Hägglund, T. (2014). Low-order feedforward controllers: Optimal performance and practical considerations, *Journal of Process Control*, vol. 24(9), 1462-1471

Hegedus, E.T., Birs, I.R., Ghita, M., Muresan, C.I. (2022). Fractional-Order Control Strategy for Anesthesia–Hemodynamic Stabilization in Patients Undergoing Surgical Procedures, *Fractal Fract.*, vol. *6,* paper id 614.

Van Heusden, K., Ansermino, M., Dumont, G. (2018). Robust MISO control of propofol-remifentanil anesthesia guided by the NeuroSENSE monitor, *IEEE Transactions on Control Systems Engineering*, vol. 26 (5), pp. 1758–1770.

Merigo, L., Padula, F., Latronico, N., Paltenghi, M., Visioli, A. (2019). Optimized PID control of propofol and remifentanil coadministration for general anesthesia, *Commun. Nonlinear Sci. Numer. Simul.*, vol. 72, pp. 194–212.

Mihai, M., Birs, I.R., Hegedus, E., Copot, D., Neckebroek, M., De Keyser, R., Ionescu, C.M., Muresan, C.I. (2024). A compact fractional-order model for hypnosis in general anesthesia, *12th IFAC Conference on Fractional Differentiation and its Applications*, Bordeaux, France, July 9-12, 2024, under review

Schiavo, M., Consolini, L., Laurini, M., Latronico, N., Paltenghi, M., Visioli, A. (2021). Optimized feedforward control of propofol for induction of hypnosis in general anesthesia, *Biomedical Signal Processing and Control*, vol. 66, paper id 102476.

Schiavo, M., Padula, F., Latronico, N., Paltenghi, M., Visioli, A. (2023). Experimental results of an event-based PID control system for propofol and remifentanil coadministration, *Control Engineering Practice*, vol. 131, paper id 105384.

Nunes, C.S., Mendonça, T., Lemos, J.M., Amorim, P. (2009), Feedforward adaptive control of the Bispectral Index of the EEG using the intravenous anaesthetic drug propofol, *Int. J. Adapt. Control Signal Process*., vol. 23, pp. 485-503.

Soltesz, K., Van Heusden, K., Dumont, G.A. (2020), Models for control of intravenous anesthesia. In Copot, D., *Automated Drug Delivery in Anesthesia*, pp. 119-166. Academic Press.

Wheeler, P., Hoffman, W.E., Baughman, V.L., Koenig, H. (2005). Response entropy increases during painful stimulation, *Journal of Neurosurgical Anesthesiology*, vol. 17(2), pp. 86–90