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A μ-synthesis-based Approach to Automate Opioid Injection in Post-surgery Patients

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Abstract— **This paper presents a robust control design for the automation of opioid injection in post-surgery patients. Most medical devices in today's hospitals interact with each other over a network. However, owing to their complexity, these interconnected devices usually lack a reliable automated control system, and are still manually supervised and controlled by a human caregiver. The risk of human caregiver errors remains high during medical procedures, and often results in unexpected health issues for the patients. Therefore, in the present paper, we attempt to design a robust feedback controller for an analgesia infusion pump. The plant consists of the patient's body connected to an infusion pump actuator. A μ-synthesis-based method is employed in order to design a robust controller to regulate the amount of drug injected into the patient's body, while maintaining the heart rate and blood oxygenation of the patient at a safe level. The controller is designed such that it remains robust to all uncertainties in the patient model that emerge as a result of diversity in the human population. We consider noisy measurements of vital signs in order to show the improvements and reliability of the closed-loop system under practical conditions. Promising results are obtained and discussed at the end of the paper.**

I. Introduction

In a modern hospital, there is a wide variety of monitoring and treatment devices that play a crucial role in the patient's treatment. In order to guarantee the patient's safety, which is the most important part of the treatment, all measurements should be evaluated accurately and all devices should perform precisely. Yet, reasoning about the patient's safety is very difficult because of insufficient knowledge of the dynamics of the human body's response to treatment. In addition, by increasing the number of sensors and medical devices used in the treatment process, the burden on the caregiver as the person responsible for the patient's health has been increased. Hence, human caregiver errors is one of the main concerns facing the healthcare sector.

From a control system's point of view, the patient's body can be seen as an open-loop system while the monitoring and treatment devices play the roles of sensors and actuators, respectively. The caregiver is the controller in the closed-loop system who uses the data obtained from sensors in order to adjust the actuating devices. But this conventional control system is not reliable enough to ensure the patient's safety. As reported in the literature [1], this conventional medical system may put the patient's safety in danger because of the multitude of possible human errors. High level of uncertainty in the patient's dynamic model, existence of disturbance in measurement devices, and limited expert work force are factors that convinced researchers to think about employing automatic controllers in place of human controllers. Currently though, there are only a few medical devices that use automatic controllers [2]. The potential for applying such controllers exists, as many medical devices today have network interfaces and can send sensed data across the network. The human caregiver could be employed as a supervisor and play a role only in cases of emergency.

Some early studies have been conducted for automatic control of blood pressure through the regulation of vasoactive drugs and validated using animal trials. Most of these early studies employed PID controllers [3], [4]. Others including Koivo [5], [6] employed automatic control methods that were essentially non-adaptive. It is noteworthy here that the key concern in letting automatic controllers make judgements is the high level of variation in the vital signs across patients belonging to different populations. Conventional control methods like PID controllers have poor robustness when the system has specific levels of uncertainties. These controllers can usually achieve control objectives only at specific operating conditions, or in this case, for a special class of patients for whom the controllers have been tuned. When the system model includes certain levels of uncertainties, either an adaptive or a robust control approach is required in order to ensure closed-loop system stability and performance in the presence of those uncertainties. Although adaptive control techniques can be effective, they require constant update of the plant model in order to adjust the controller, thereby requiring system identification and modeling for controller tuning. On the other hand, $\mathscr{H}_\infty$ control approaches may achieve robust stabilization against unstructured system perturbations and nominal performance requirements. However, their efficiency in case of structured uncertainties becomes limited. Owing to this reason, in this paper, we choose robust control design methods based on *structured singular values* (SSV) in order to achieve robust performance. We design a robust controller based on the so-called μ-*synthesis* for the pump connected to the patient's body. The controller is required to adjust the drug level in the patient's blood plasma in order to prevent an over-dose, which can often lead to respiratory failure. In order to ensure

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the patient's safety, all uncertainties regarding the patient's body dynamics are considered in the plant modeling. The proposed controller can cope with uncertainties and reject the disturbances while adjusting the drug injection rate in order to maintain the drug level in the patient's body.

The rest of this paper is organized as follows. The problem is described and formulated in Section II. In Section III, robust controller design procedure using μ-synthesis is presented. Section IV provides numerical simulation results. Finally, Section V provides some concluding remarks.

II. Problem Statement

The injection of pain relieving drugs, or opioids, in post-surgery patients requires a critical analysis of the patients' vital signs, as an overdose of opioid medication can often lead to respiratory failure. Moreso, different patients react differently to pain medication; consequently, the dose of opioids given to a patient varies highly from one case to another. Hence, opioids are generally injected using a patient-controlled analgesia (PCA) pump [1]. These pumps provide a button to the patient, who can press it in order to request pain relievers. The dose is finally injected under the supervision of a caregiver. Steps to automate this procedure have been studied in detail in papers like [1], in which the authors simulated case studies and concluded that under no failure assumptions, closed-loop medical systems would generally be safe. However, to the best of our knowledge, control design for the automation of closed-loop drug injection remains an open problem.

A big motivation for automating this procedure lies in the sensitivity of the process and the possible sources of error in a patient-controlled caregiver-supervised arrangement. Some patients often receive over-dose due to misprogrammed pumps, over-estimation of dosage by the programmer, or accidental pressing of the button by someone other than the patient. Such mishaps have occurred more frequently than expected or desired [7], [8].

In a typical caregiver-supervised opioid injection system, an oxymeter is used to record the relevant vital signs of the patient like blood oxygenation level S_{pO_2}, heart rate r_h, and the level of drug l_d in the blood plasma of the patient [9]. The patient model taken from [1], [10] is given as

$$\begin{bmatrix}\dot{C}_1\\ \dot{C}_2\\ \dot{C}_3\end{bmatrix} = \begin{bmatrix}-(k_{12}+k_{13}+k_{10}) & k_{21} & k_{31}\\ k_{12} & -k_{12} & 0\\ k_{13} & 0 & -k_{31}\end{bmatrix}\begin{bmatrix}C_1\\ C_2\\ C_3\end{bmatrix} + \begin{bmatrix}\frac{1}{V_1}\\ 0\\ 0\end{bmatrix} I,$$

$$l_d = \begin{bmatrix}1 & 0 & 0\end{bmatrix}\begin{bmatrix}C_1\\ C_2\\ C_3\end{bmatrix}. \tag{1}$$

Model (1), also shown in Figure 1, is known as the 3-compartment pharmacokinetic model, and is used in the study of the dynamic behavior of drug concentrations in blood and tissues. In the said model, state variables $C_i, i \in \{1,2,3\}$ represent drug concentration in the i^{th} compartment of the patient's body, I is the drug mass infusion rate (mass/unit time), and coefficients k_{ij} are patient specified constants. These coefficients vary from patient to patient depending upon the genetics of the patient; hence, these coefficients can be considered varying around specific nominal values. Measurable output variable l_d represents drug level in the blood plasma compartment. The volume of the blood plasma compartment, C_1, is denoted by V_1. It is assumed that the drug is directly infused into this compartment. The drug then diffuses between compartment 1 and compartments 2 and 3 based on the transfer parameters k_{ij}. Compartment 2 represents well-perfused tissues, such as muscle and brain, while compartment 3 represents residual tissues and bones. Together, the 3-compartment pharmacokinetic model describes the dynamic behavior of the drug, as it is infused into the blood plasma and consequently absorbed into muscles, bones and tissues. The absorption parameters k_{ij} can vary from patient to patient as different bodies absorb drug at different rates [10]. Variables k_{ij} and V_1 represent uncertain varying parameters in the patient model and are given as

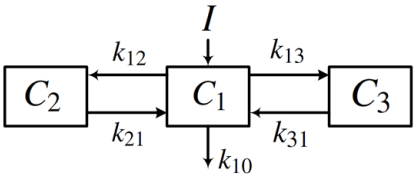

Fig. 1. A 3-compartment pharmacokinetic model of a post-surgery patient. Compartments C_i represent plasma compartment, well-perfused tissues and residual tissues for $i = 1, 2$, and 3, respectively. Variable I represents infusion rate of the drug, usually injected directly into C_1.

$$\begin{aligned} k_{ij} &\in \left[\bar{k}_{ij} - \Delta k_{ij}, \bar{k}_{ij} + \Delta k_{ij}\right],\\ V_1 &\in \left[\bar{V}_1 - \Delta V_1, \bar{V}_1 + \Delta V_1\right], \end{aligned} \tag{2}$$

where $\bar{k}_{ij}$ and $\bar{V}_1$ represent the nominal values, while Δk_{ij} and ΔV_1 represent the range of variation [11]. The patient's S_{pO_2} and heart rate are related to the drug level l_d via a drug absorption function. The drug absorption function can also exhibit uncertainty owing to the variation in responses among different patients. For the sake of simplicity, however, here as in [1], a fixed linear mapping is considered for the drug absorption function as

$$\begin{aligned} r_h &= 80 - 0.8 l_d,\\ S_{pO_2} &= 100 - 0.35 l_d, \end{aligned} \tag{3}$$

where r_h represents the heart rate. As can be seen from the drug absorption function (3), the heart rate r_h and S_{pO_2} are inversely related to the level of drug in the patient's blood plasma. A sign of drug overdose is therefore a drop in these two variables. Values of $r_h < 57$ beats/min and $S_{pO_2} < 90\%$ are considered "alarming" and constitute as a clinical concern [12]. Values of $r_h < 11.5$ beats/min and $S_{pO_2} < 70\%$ are

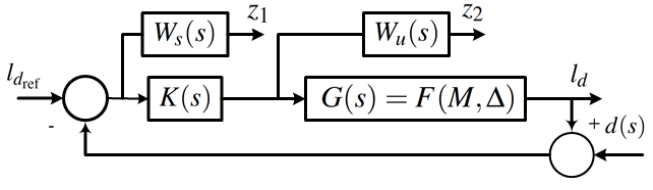

Fig. 2. Closed-loop system interconnection with controller $K(s)$ and post-surgery patient described by the model transfer function $G(s)$; variable $d(s)$ represents measurement noise.

considered a clear indication of an impending respiratory failure [1]. To avoid the alarming heart rate $r_h = 57$, a maximum drug level threshold of $l_d = 28.75\mu g/ml$ should not be exceeded. Similarly, $S_{pO_2} = 90\%$ maps to a maximum $l_d = 28.57\mu g/ml$.

Given the nominal model, the range of uncertainties, and a basic knowledge of the patient's important measurements, we can then formulate the problem as follows

"*Design a controller that can automate the opioid drug injection procedure such that the desired level of drug concentration l_d in the patient remains at or close to a set-point that keeps the patient's heart rate r_h and blood oxygenation level S_{pO_2} outside the alarming region. The controller should be robust to uncertainties in the patient model pertaining to different populations of patients. The design objective is that the closed-loop system should be stable and guarantee an acceptable quadratic performance measure.*"

Figure 2 shows a basic closed-loop control structure. The required controller is represented by $K(s)$, while the patient is represented by the uncertain model $G(s)$; variable d represents measurement noise, while $W_s(s)$ and $W_u(s)$ are weighting filters that are chosen as part of the controller synthesis and design procedure.

III. Robust Controller Design Procedure

For uncertain systems, most often a robust controller design is sought in order to stabilize the system while simultaneously achieving certain performance criteria under all values of the uncertain parameters. Designs involving $\mathscr{H}_\infty$ loop shaping based on *small gain theorem* (SGT) have been established as efficient robust design methods for LTI systems; however, they can usually achieve robust stabilization only against unstructured system perturbations [13]. For structured or parametric uncertainties, there is no guarantee of achieving an acceptable robust performance; this renders methods based on SGT mostly unapplicable to problems like opioid injection control problem. In order to achieve robust stabilization and robust performance for such problems, methods based on *structured singular value* (SSV) can be used. These methods have shown considerable improvements in achieving robust performance requirements as compared to H_∞-based methods [14]. In this section, we review μ-synthesis-based robust controller design employing the so-called D-K iterative algorithm and show how to formulate it for the patient model.

A. Structured singular values

The conditions derived for robust stabilization using SGT can be very conservative for systems with structured uncertainties. To cope with such systems, SSV was introduced in [15], and will be briefly described here. Assume that the nominal system is stable; then, based on SGT, robust stabilization condition for the system in *linear fractional transformation* (LFT) representation (see Figure 4 (c)) can be written as [13]

$$\det[I - M(j\omega)\Delta(j\omega)] \neq 0,\ \forall\omega \in R,\ \forall\Delta, \tag{4}$$

where $M(s)$ and $\Delta(s)$ denote the nominal system and the uncertainties in the standard LFT representation. This condition is necessary and sufficient, even for structured uncertainties. In other words, for an uncertain system, all uncertainties should be small enough not to make $(I - M\Delta)$ singular at any given frequency. For a given nominal system M with a fixed controller K and a known structure of the uncertainties, the smallest size of uncertainty that causes $(I - M\Delta)$ to become singular at some frequency describes how robustly stable the controller K is in dealing with such structured uncertainties. This leads us to the definition of SSV given below. Consider the following uncertainty

$$\Delta = \{\mathrm{diag}(\delta_1 I_{r1}, \ldots, \delta_s I_{rs}, \Delta_1, \ldots, \Delta_f) \mid \delta_i \in C, \Delta_j \in C^{m_j \times m_j}\}, \tag{5}$$

where $\delta_i I_{ri}$ represents the i^{th} structured uncertainty block with the dimension r_i, Δ_j represents the j^{th} unstructured uncertainty block, and $\Sigma_{i=1}^{s} r_i + \Sigma_{j=1}^{f} m_j = n$, with n being the dimension of the uncertainty matrix Δ. Also, it is assumed that the set $\mathbf{\Delta}$ is bounded. The normalized set of structured uncertainty can then be defined as

$$B\mathbf{\Delta} = \{\Delta \mid \overline{\sigma}(\Delta) \leq 1, \Delta \in \mathbf{\Delta}\}, \tag{6}$$

where $B\mathbf{\Delta}$ represents a set of uncertainties scaled within a unit ball.

Definition: For $M \in C^{n\times n}$, the structured singular value $\mu_\Delta(M)$ with respect to $\mathbf{\Delta}$ is the inverse of the smallest $\overline{\sigma}(\Delta)$ that results in a rank deficient matrix $(I - M\Delta)$ or

$$\mu_\Delta^{-1}(M) := \min_{\Delta \in \mathbf{\Delta}} \{\overline{\sigma}(\Delta) \mid \det(I - M\Delta) = 0\}. \tag{7}$$

If there is no $\Delta \in \mathbf{\Delta}$ such that $\det(I - M\Delta) = 0$, then $\mu_\Delta(M)$ is equal to zero.

Theorem [16]: *For the system in Figure 4(a), with stable nominal system $M(s)$, let us consider $\beta > 0$ to be an uncertainty bound such that $||\Delta||_\infty < \beta$; the perturbed system is robustly stable with respect to $\mathbf{\Delta}$ if and only if $\mu_\Delta(M) < \beta$.*

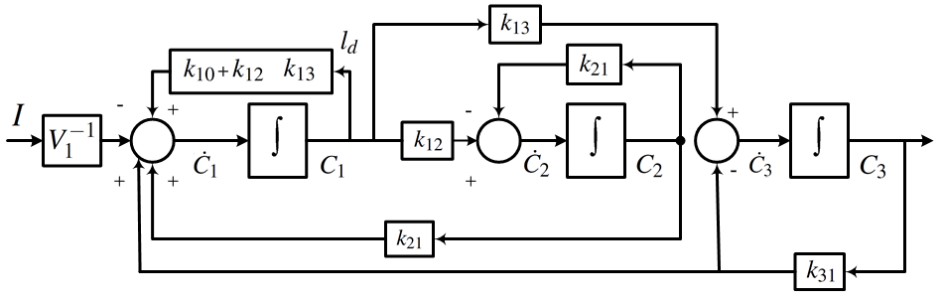

Fig. 3. Block diagram of nominal dynamic patient model

The SSV plays an important role in a robust design. Firstly, because it is able to deal with structured uncertainty for robust stabilization; secondly, it enables us to transform a robust performance design into a robust stabilization problem with regard to the structured uncertainty. For further details on SSV, the interested reader is referred to [13].

B. Robust performance and μ-synthesis

Robust performance requires that a controlled system maintains a satisfactory performance level in the presence of uncertainties. For the configuration shown in Figure 4(a), w denotes exogenous inputs typically including reference inputs, disturbances, and noise; z denotes signals including regulated outputs, tracking errors, and filtered control inputs; v and d are the input and output signals of the dynamic uncertainties. With the assumption that w and z are both energy-bounded signals, the system performance requirement is usually equivalent to the minimization of H_∞ norm of the transfer function from w to z. Let M be partitioned accordingly as

$$M = \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix}. \tag{8}$$

Then, we can write the following

$$z = [M_{22} + M_{21}\Delta(I - M_{11}\Delta)^{-1}M_{12}]w = F_u(M,\Delta)w. \tag{9}$$

Using normalization, a satisfactory level of performance requirement can be set as

$$\|F_u(M,\Delta)\|_\infty < 1 \tag{10}$$

Inequality (10) is equivalent to robust stability subject to a fictitious uncertainty block Δ_p as shown in Figure 4(b). This fictitious uncertainty is named performance uncertainty block and is unstructured with appropriate dimension such that $\|\Delta_p\|_\infty \leq 1$. Roughly speaking, robust performance and stabilization design can be unified as a robust stabilization problem of the system in Figure 4(c) w.r.t. $\widetilde{\Delta}$, where

$$\widetilde{\Delta} \in \widetilde{\mathbf{\Delta}} = \{\mathrm{diag}(\Delta, \Delta_p) \mid \Delta \in B\mathbf{\Delta}, \|\Delta_p\|_\infty \leq 1\}. \tag{11}$$

This unification makes the problem that of robust stabilization with respect to a structured $\widetilde{\Delta}$.

C. D-K iterative approach for robust controller design

In order to design the controller, Figure 4(c) should be rearranged to explicitly show the dependency of the closed-loop system on the controller K, where $P(s)$ is the nominal open-loop interconnected transfer function matrix that can be partitioned as

$$P(s) = \begin{bmatrix} P_{11} & P_{12} & P_{13} \\ P_{21} & P_{22} & P_{23} \\ P_{31} & P_{32} & P_{33} \end{bmatrix}. \tag{12}$$

The relationship between M and P could be presented as

$$M(P,K) = F_l(P,K) = \begin{bmatrix} P_{11} & P_{12} \\ P_{21} & P_{22} \end{bmatrix} + \begin{bmatrix} P_{13} \\ P_{23} \end{bmatrix} K(I - P_{33}K)^{-1} \begin{bmatrix} P_{31} & P_{32} \end{bmatrix}. \tag{13}$$

For robust stability and performance requirements, the goal is to find a stabilizing controller K such that

$$\sup_{w \in R} \mu[M(P,K)(j\omega)] < 1. \tag{14}$$

For optimal design, the following optimization problem needs to be solved

$$\inf_K \sup_{w \in R} \mu[M(P,K)(j\omega)]. \tag{15}$$

D-K iteration for μ-synthesis has been described in detail in [14]. Briefly speaking, the D-K approach is based on solving the following optimization problem for a stabilizing controller K and a diagonal constant scaling matrix D

$$\inf_{K(s)} \sup_{w \in R} \inf_{D \in \mathbf{D}} \overline{\sigma}[DM(P,K)D^{-1}(j\omega)], \tag{16}$$

where $\mathbf{D}$ is the scaling matrix set as defined in [17]. In order to approximate the required structured singular value, $\mu[M(P,K)]$ is replaced by the upper bound $\inf_{D \in \mathbf{D}} \overline{\sigma}[DM(P,K)D^{-1}]$ in (16). Further details about the calculation of SSV and the application of D-K iteration-based μ-synthesis can be found in [14], [16], [18]. In this paper, we employ the said control synthesis design by using MATLAB® Robust Control Toolbox [19].

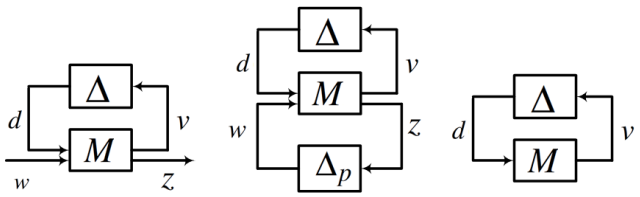

Fig. 4. Standard $M-\Delta$ configuration: (a) for robust performance analysis, (b) with fictitious uncertainty Δ_p, and (c) for robust stability analysis

D. Drug infusion problem using μ-synthesis

A block diagram of the nominal patient model is shown in Figure 3. Because of the variations in the patient's dynamic model, the parameters of this model can vary from patient to patient. It can, however, be assumed that these values are within certain known intervals. All of these uncertain blocks can be represented in an upper LFT form. We therefore replace each nominal block k_{ij} and V_1^{-1} in Figure 3 with an uncertain system in an upper LFT interconnection as shown in Figure 4(a). To obtain the LFT representation of the whole system, MATLAB® system interconnection command `sysic` is used.

$$u(s) = K(s)y(s), \tag{17}$$

that guarantees the following properties:

Robust stability: The closed-loop system should be stable for all possible plant models $G = F_u(M,\Delta)$, if the open-loop system is internally stable.

Robust performance: The closed-loop system for all $G = F_u(M,\Delta)$ must satisfy the performance criterion

$$\left\| \begin{matrix} W_s(I+GK)^{-1} \\ W_uK(I+GK)^{-1} \end{matrix} \right\|_\infty < \gamma. \tag{18}$$

The weighting functions W_s and W_u (see Figure 2) are used to reflect the relative significance of the performance requirements over different frequency ranges. W_s is usually chosen to be a low pass filter; W_u is chosen to be a high pass filter or a static gain to penalize the control inputs over a desired frequency range. Together, these two filters are referred to as loop-shaping filters that shape the sensitivity matrix $(I+GK)^{-1}$ and control sensitivity matrix $K(I+GK)^{-1}$ of the closed-loop system.

As elaborated in the previous section, to design a controller that satisfies robust performance, the performance requirements are translated to a fictitious uncertainty block that should be added to the uncertain system representation. As there are two performance requirements and one input, the uncertainty block structure is defined as

$$\tilde{\Delta} = \left\{ \begin{bmatrix} \Delta & 0 \\ 0 & \Delta_p \end{bmatrix} : \Delta \in \mathbb{R}^{6\times 6}, \Delta_p \in \mathbb{R}^{1\times 2} \right\}. \tag{19}$$

The first uncertainty block Δ of this structured matrix is diagonal and corresponds to the parametric uncertainties in the patient model. The second block Δ_p is a fictitious or performance uncertainty block that is introduced to represent the performance requirements in the framework of μ-synthesis. Once the uncertainty blocks are defined, the optimization problem (15) is solved with respect to K in order to minimize the upper bound of μ.

TABLE I

OUTPUT OF THE D-K ITERATION ALGORITHM

Iteration #	1	2	3	4
Controller order	4	8	10	14
γ achieved	1.734	0.976	0.978	0.976
Peak μ-value	1.444	0.975	0.973	0.971

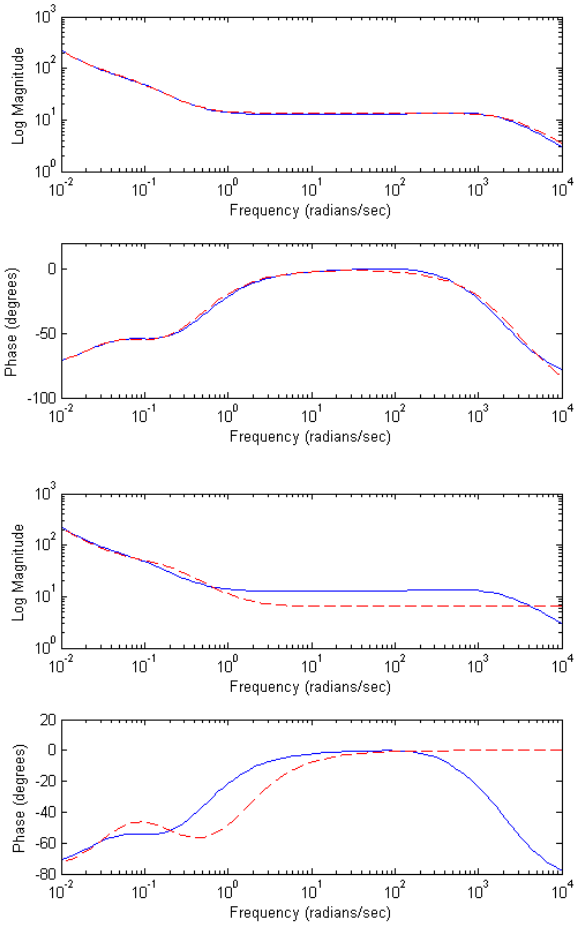

Fig. 5. Comparison of Bode plots of 14th order controller with that of (top) 3rd and (bottom) 2nd order controller.

IV. Simulations Results and Discussion

Having separated out the structured uncertainties, we use MATLAB® command `sysic` in order to obtain an upper LFT form of the uncertain system. The nominal values of the model parameters k_{ij} are taken from [1], [9] as

$$\bar{k}_{10} = 0.152 \text{ min}^{-1},\ \bar{k}_{12} = 0.207 \text{ min}^{-1},\ \bar{k}_{13} = 0.04 \text{ min}^{-1},$$
$$\bar{k}_{21} = 0.092 \text{ min}^{-1}, \bar{k}_{31} = 0.048 \text{ min}^{-1},\ \bar{V}_1 = 12 \text{ liters}.$$

Variations Δk_{ij} and ΔV_1 are taken as 8% of their respective nominal values. We then run the D-K iteration algorithm employing the MATLAB® `dkit` function in order to obtain a μ-synthesis controller. For the purpose of loop shaping, we use a first order low pass filter $W_s(s) = \frac{0.5}{s+0.01}$ to achieve steady state tracking. We also use a gain $W_u(s) = 10^{-6}$ on the controller output. These weights are chosen by trial and error. Additive zero-mean Gaussian noise is added at the measurement output such that a signal-to-noise ratio (SNR) of 20dB is maintained. The D-K iteration algorithm output is shown in Table I. After 4 iterations, the best peak μ value achieved is 0.97, which guarantees stability. Iteration 4 gives a 14^{th} order controller. This is a fairly high order controller; therefore, we reduce the order of the controller using balanced truncation and obtain a 2^{nd} and a 3^{rd} order controller. Figure 5 shows the Bode plot comparison of the 14^{th} order controller with that of the 3^{rd} and 2^{nd} order controllers. The reduced 3^{rd} order controller gives an exactly matching frequency response; the reduced 2^{nd} order controller shows mismatch at higher frequencies. We, therefore, reduce the controller order to three for the purpose of reference tracking, and simulate the closed-loop drug injection system with this controller. We randomly generate the uncertain parameters k_{ij} and V_1 in the specified range. A desired drug level of below 28.5 $\mu g/ml$ is chosen as the reference signal. Figure 6 shows the controlled drug level in five different patients with different perturbation parameters k_{ij} and V_1. The figure also shows the drug injection rate. In each of the five cases, the obtained controller successfully stabilizes the drug level to the desired set-point, ensuring that the patient remains safely outside the alarming region. This assures us that the drug level can be regulated to a pre-defined reference value regardless of the uncertainty accompanying the patient.

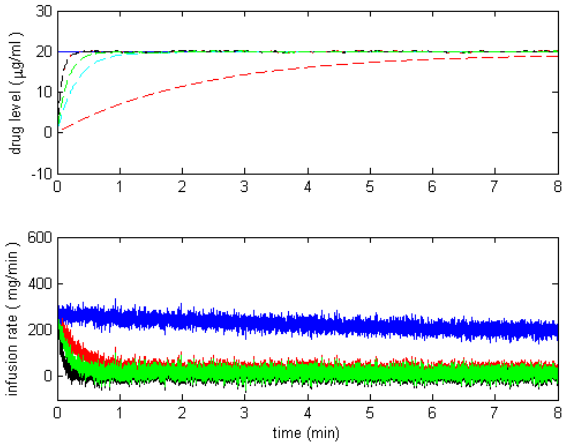

Fig. 6. Closed-loop simulation results for five randomly generated models of different patients showing: (top plot) controlled level of drug in patient blood plasma and (bottom) drug injection rate as the controller output.

V. Concluding Remarks

In this paper, we designed a robust μ-synthesis-based controller that can regulate opioid level in post-surgery patients in order to keep the patient safe from an opioid over-dose. The real challenge lies in the need for robust performance. The considered human model has six uncertain parameters. Using D-K iteration algorithm, we were able to obtain a 14^{th} order controller guaranteeing drug-level stability. The obtained closed-loop system was shown to provide a quadratic performance $\gamma = 0.976$. We further employed balanced truncation in order to reduce the said controller to a 3^{rd} order controller. Closed-loop simulation results illustrate stabilization and noise rejection for five different patients while achieving reference tracking, and provide a promising insight into the future realization of automated drug regulation in post-surgery patients.

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