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Robust System Identification for Anemia Management

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Abstract: Anemia is the condition in which patients suffer from the deficiency of the red blood cells to carry the oxygen in the body. One of the many causes of anemia is chronic kidney disease (CKD). CKD is a disease in which kidneys are partially or completely damaged, which results in a deficiency of the oxygen-carrying red blood cells. CKD is common in older people, and external human recombinant erythropoietin (EPO) is required to maintain healthy levels of hemoglobin (Hb). In order to effectively address the impact of inter and intra-individual variability in dose-response characteristics in CKD patients, individualized patient-specific models are required instead of traditional population-based models. In this research, individualized patient models are developed by using patient-specific time-domain data with robust system identification techniques. For control-oriented system identification, two robust identification techniques are investigated: (1) l_1 robust identification considering zero initial conditions and (2) Semi-blind robust system identification considering non-zero initial conditions. The performance of these two techniques is compared and it is shown that the Semi-blind robust identification technique gives better results as compared to l_1 robust identification.

Keywords: l_1 robust system identification, Semi-blind robust system identification, Robust system identification, Anemia management, Chronic kidney disease.

1. INTRODUCTION

In recent years, the need for drug management in bio-engineering is becoming one of the prominent applications for control systems researchers. In chronic kidney disease (CKD), the kidneys are partially or completely damaged and not able to produce enough erythropoietin, a glycoprotein that produces red blood cells (ADAMSON, 1968), this results in the reduced number of oxygen-carrying red blood cells in the human body, this condition is called anemia. The patients of this disease are treated with recombinant human erythropoietin (EPO). The dosage of EPO to the human body increases the hemoglobin (Hb) levels (Eschbach and Adamson, 1985). According to the National Kidney Foundation's Dialysis, the Hb level should be in the range of 11 and 12 g/dL in the response of EPO dosage (Valderrábano, 1996).

Presently, the medical centers have developed their own anemia management protocols (EPO management systems) based on the average (population-based) response medication. While population models may be useful in the analysis of drug properties at large, they are not well suited to guide the treatment of individual patients. To effectively address the impact of inter and intra-individual variability in dose-response characteristics, personalized, patient-specific models are needed. Therefore, medical institutes need a stable and robust system for individualized anemia management. The key point in designing an efficient individualized anemia management system is to find accurate patient-specific dose-response models.

Many researchers have attempted to develop patient models for anemia management. Bayesian-based drug delivery using population patient data is discussed in (Bellazzi, 1993). Artificial Intelligence-based neural network models are discussed in (Gaweda et al., 2003) (Guerrero et al., 2003) (Gaweda, 2009). Some researchers attempted to identify individual patient models in (Muezzinoglu, 2006). In (Martín-Guerrero et al., 2003) the main focus was to predict the value for EPO instead of Hb, which is not desired as predicting Hb level gives values of EPO but is not true for the opposite. However, most of these models are based on predetermined model structure and noise distribution, which is not suitable for anemia management as each patient poses different model characteristics.

The models obtained by the classical system identification techniques generally do not yield good results as they assume that predefined model structure and model order are close to the actual plant (patient) and one mathematical model works for all patients regardless of complexity and disturbances in the plant. The modeling stage should include the effect of all uncertainties, which are being introduced during operations. In contrast to classical identification techniques, robust system identification takes into account system uncertainties, unmodeled dynamics, and model complexity, i.e., there is no assumption on the model order, uncertainties, and noise affecting data.

The robust control design requires the nominal model and uncertainty bound on the model (Ljung, 1999). Therefore, system identification techniques should provide a nominal model and uncertainty bound on it. The robust system identification procedure does not require large measurement data set or information of measurement noise, nor the information on the structure of the plant/patient model to be identified is required (Sánchez Peña and Sznaier, 1998) (Mazzaro et al., 2001). In robust identification, the information on the maxi-

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mum gain of the system K, the stability margin of the system response ρ, and bound on the noise are required. Depending on the nature of the a posteriori information, the robust identification techniques may lead to different identification methods. The selection of robust system identification method depends on the data type as time-domain data and frequency domain data pose different characteristics, and different techniques are applied to obtain a model for the data type (Schoukens et al., 2010). For frequency domain data, the H_∞-identification technique is implemented, which calculates the uncertainty bounds in terms of the H_∞-norm (Chen and Gu, 2000). For time-domain data, the l_1-identification technique is implemented, which calculates an l_1-error bound (Akabua et al., 2011)(Akabua et al., 2015). However, sometimes both time and frequency domain data may be available for a single plant. In this case, the mixed H_∞/l_1 robust identification procedure is used (Inanc et al., 2001) (Chen and Nett, 1993).

In this research work, the individual patient model for anemia management is obtained using robust system identification techniques and time domain patient-specific data. For system identification, the l_1 robust system identification and Semi-blind system identification techniques (Ma, 2006) are used. The plant/patient model is a combination of a nominal model and uncertainty bound. Both of these identification techniques, develop a nominal model and uncertainty bound using patient-specific dose-response (EPO-Hb) data.

We summarize our contributions as follows:

(1) We present an individualized patient model for anemia patients using l_1 robust system identification assuming zero initial conditions. The patient model is reduced to appropriate order which is suitable for control synthesis techniques.
(2) We present an individualized patient model for anemia patient using Semi-blind robust system identification by incorporating the effects of initial conditions instead of assuming it zero.
(3) The prediction accuracy of the patient models obtained by the both techniques is compared using minimum mean squared error (MMSE) analysis.

The remainder of this paper is organized as follows. First, we discuss the l_1 robust system identification in Section 3. Then, we introduce the Semi-blind robust system identification in Section 4. Finally, we present the models for different patients and prediction results obtained by the one-step-ahead prediction along with the error analysis for both techniques in Section 5 followed by the conclusion.

2. SYSTEM IDENTIFICATION

The plant (patient) model is the set of mathematical equations that describes the plant (patient) behavior in response to the input. In this work, the system model G is the combination of a parametric and non-parametric portion given as:

$$G = G_p + G_{np} \tag{1}$$

The non-parametric portion G_{np} describes the internal behavior of the plant. This portion requires less prior knowledge of the system, such as a model for the internal behavior of physiological systems. On the other hand, the parametric portion G_p describes the input to output relation. In anemia management, it is important to take into account that patient may have medical history due to other diseases and medications. It is also important to mention that for this application, the patient data is not steady state-data, therefore, the effect of past inputs is still present. To reduce the error in identification, it is important to use the initial conditions in the model identification process for the application of anemia management. To incorporate the effect of initial conditions, the Semi-blind identification technique is introduced, which uses the same framework as l_1 robust identification but also includes the effects of past inputs. Next, we formally define the problem.

Problem 1. Considering 2, obtain the patient model G, which gives output y_i as Hb level in response to input u_i of EPO dosage to patients of CKD.

$$y_i = Gu_i + \eta_i, \tag{2}$$

$$|\eta_i| \leq \epsilon_i, \tag{3}$$

where η_i is the noise, which is unknown but bounded, and ϵ_i is the maximum bound on noise.

3. l_1 ROBUST IDENTIFICATION

The l_1 robust identification obtains a patient model with minimum prior knowledge about patient (Dahleh et al., 1993). The classical identification techniques assume that the model has a fixed order and structure and probabilistic noise distribution. However, l_1 robust identification does not assume a fixed order model or noise distribution (Jacobson and Nett, 1991). It requires minimal prior information, such as the maximum gain on the system $K > 0$, the lower bound on the relative stability margin of the patient dynamics $\rho > 1$, and an upper bound on the noise in measurements $\epsilon > 0$ (Akabua et al., 2015). Consider a linear time-invariant (LTI) operator g of system class S, which maps u from input space to y in output space. The impulse response of g is given as follows:

$$G(z) = \sum_{i=0}^{\infty} g_i z^{-i}, g_i = K\rho^{-i}, \tag{4}$$

By the discussion, for N samples of data, the robust identification problem can be defined as follows:

Problem 2. Given the a priori and the a posteriori information, determine:

- whether the priori and posteriori information are consistent, i.e decide whether the models in $G_{\infty,\rho}$ interpolates the given measurement points with error bounded by the priori error information. The priori and posteriori information is consistent if and only if, Γ is a non-empty set.

$$\Gamma \doteq g \in S|_{y_i} = (g * u_i) + \eta_i \tag{5}$$

- If the two sources of information are consistent, then obtain such a model as well as a bound on the worst-case identification error.

The consistency is determined by using Carathêodory-Fejér Interpolation (Lim et al., 2003), defined below:

Problem 3. Given sequence of complex points, g_i where $i = 0, 1, \cdots N-1$, determine a function $G(z)$ such that

$$G(z) = g_0 + g_1 z^1 + g_2 z^2 + \cdots + g_{N-1} z^{N-1} + \hat{g}_N z^N \tag{6}$$

The solution of this problem consists on the following inequality.

$$I - T_g^* T_g \geq 0, \tag{7}$$

where T_g it the nxn lower triangular Toeplitz matrix of sequence $\{g_0, g_1, \cdots g_{n-1}\}$. The solution of Carathêodory-Fejér

Interpolation exits only if vector $g = g_0 + g_1 z^1 + g_2 z^2 + \cdots + g_{N-1} z^{N-1}$ exists such that following Linear Matrix Inequality (LMI) holds:

$$M(g) = \begin{bmatrix} KR^{-2} & (T_g^N)^T \\ (T_g^N) & KR^2 \end{bmatrix} \geq 0,$$
$$\left| y - T_u^N g - T_u^N pP \right| \leq \epsilon,$$

where R is the diagonal matrix with coefficients $\{1, \rho, \cdots \rho^{N-1}\}$ and P is the parametric portion of the model. The T_u^N and T_g^N are the nxn upper triangle matrix with coefficients $\{u_o, u_1, u_2, \cdots u_{N-1}\}$ and $\{g_o, g_1, g_2, \cdots g_{N-1}\}$, respectively.

In l_1 robust system identification (Sánchez Peña and Sznaier, 1998) (Inanc et al., 2001), the initial conditions are considered as zero, is suitable for non-parametric estimation. However, to be able to include the effect of the initial conditions in the patient model, the Semi-blind robust identification technique is introduced in Section- 4.

4. SEMI-BLIND SYSTEM IDENTIFICATION

The response of patient models is affected by its state at $t = 0$, such as prior health conditions and medications. To include the initial condition effects, the identification technique described in Section 3 needs to be improved. The Semi-blind robust identification technique takes into account information about the initial conditions of the plant (patient) (Ma et al., 2005). The problem statement for Semi-blind identification can be defined as follows:

Problem 4. Given input sequence u, output sequence y, noise bound $\in \mathcal{N}$, maximum stability gain and characteristics of past input u^-, determine $G(z) = G_p(z) + G_{np}(z)$ which is compatible with priori and posteriori information, such that τ is a non-empty set.

$$\tau(y) \doteq y_i = \sum_{i=0}^{N} g_i u_{N-i} + C_g A_g^{N-1} (\Gamma_g^N u^-)_{i=0} \qquad (8)$$

where $g_0 = D_g; g_i = C_g (A_g)^{i-1} B_g$

The solution to the (8) involves solving a Bi-Affine Matrix, which is a non-convex, NP-hard problem. The above problem can be converted to the convex problem as mentioned in (Ma et al., 2005), which preserves the controllability and observability of the system. The convex problem can be defined as follows:

Problem 5. Determine $G(z) = G_p(z) + G_{np}(z)$, which is compatible with a priori and a posteriori information, such that τ is a non-empty set:

$$\tau(y) = \left\{ G(z) \in S : y_i - (T_g^N u)_i + (\Gamma_g^N u^-)_i \right\} \qquad (9)$$

where, $\left| (\Gamma_g^N u^-)_i \right| \leqslant \gamma K_u; i = 0, 1, \cdots, N-1$ and T_g^N is the Toeplitz matrix and Γ_g^N is the Hankel matrix.

The first part of the τ set corresponds to the system response for input u and the later part provides information for system response for past inputs u^-. This problem can be solved by following the LMIs (Ma et al., 2005) (Yilmaz, 2005).

$$M(g) = \begin{bmatrix} KR^{-2} & (T_g^N)^T \\ (T_g^N) & KR^2 \end{bmatrix} \geq 0,$$
$$\left| y - (T_u^N pP + T_u^N g) - \Gamma_g^N u^- \right| \in N,$$
$$-\gamma K_u \leqslant \Gamma_g^N u^- \leqslant \gamma K_u$$

where γ, K_u, p, P represent system gain, bound K_u on the norm of the sequence u^-, affine parameters and the parametric portion of the system. Figure 1 shows the framework for Semi-blind identification. As the patient response to the EPO dosage is also affected by the past inputs u^-, the parametric part should be an integrator to accommodate all the effects of the inputs before $t = 0$, i.e initial conditions. As we have discussed,

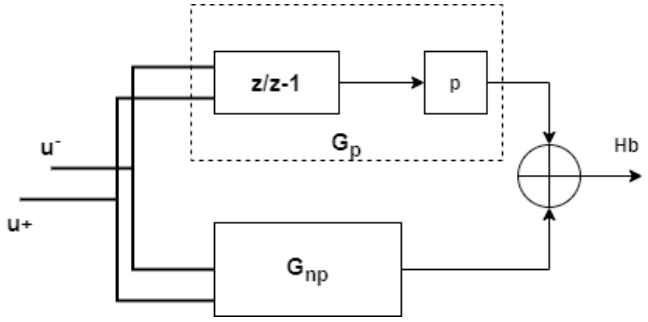

Fig. 1. Framework for Semi-blind identification.

the tools for parametric/non-parametric robust system identification to obtain a system model for the patients of chronic kidney disease for anemia management to control Hb level in response to EPO dosage. Section- 5 shows the implementation of l_1 robust identification and Semi-blind robust identification on real patient data along with system validation using one-step-ahead prediction method.

5. SIMULATION RESULTS BASED ON CLINICAL DATA

To obtain patient models using identification techniques discussed in the above sections, the EPO medication data and Hb measurement data of fifty patients have been obtained from the University of Louisville, Kidney Disease program. The EPO dosage is administrated three times a week, and the Hb level is tested only once a week. For system identification, the input/output data should be of the same length, hence three dosages of EPO per week are averaged, which corresponds to a single Hb measurement. One step ahead prediction is used to show the predicting capabilities of the identified models. The patient models obtained by the l_1 robust identification and the Semi-blind robust identification technique are compared by calculating minimum mean squared error (MMSE).

$$MMSE(k) = \frac{1}{N} \sum_{i=0}^{N} \frac{\|y(k) - \hat{y}(k)\|_2}{y(k)} \qquad (10)$$

To obtain a robust model, the parameters $\rho = 1.01$, $\eta = 0.31$ and data points $N = 5$ are used as priori information for all patients. Due to space limitations, we present the results of four patients, patient-1, patient-10, patient-21, and patient-32.

5.1 l_1 Robust Identification Results

The system model for patient number 1 obtained by l_1 robust identification and the one-step-ahead prediction is shown below:

$$G^1(z) = \frac{13.62z^3 - 5.105z^2 - 1.113z + 17.62}{z^3 - 0.03317z^2 - 0.3127z + 0.7205} \qquad (11)$$

In the following figures of l_1 robust identification results, the green line with hollow circle markers shows the actual Hb level of the patients, the blue line with dot markers shows the model

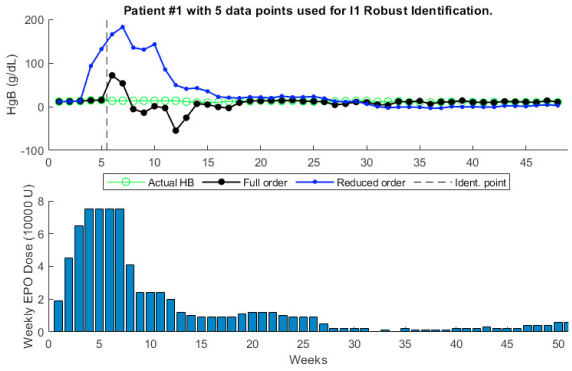

Fig. 2. Response of the patient-1 full and reduced order models obtained by the l_1 robust identification.

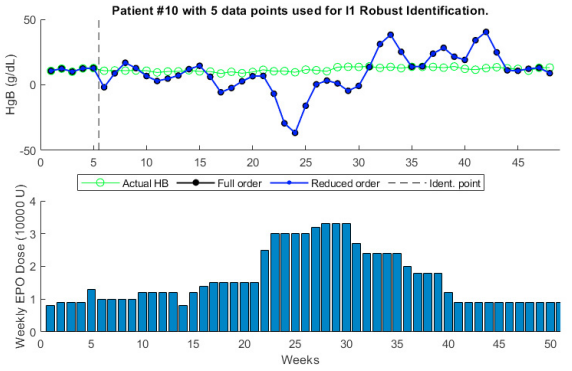

Fig. 3. Response of the patient-10 full and reduced order models obtained by the l_1 robust identification.

prediction of full order model obtained by l_1 robust identification, the blue line with dot markers shows the model prediction of the reduced order model identified using l_1 robust identification technique, and the vertical dashed line shows the number of data points used in the identification process. The vertical blue bars show the weekly EPO dosage given to the patients. The 5 samples of measurement of dose-response (EPO-Hb) data are used for the identification. After 5 samples the output is predicted by the one-step-ahead prediction. As it is seen in Fig. 2, the results of the l_1-robust identification algorithm is poor. Even for the data points used in the identification (the first 5 data points) the output of the reduced order model (3^{rd} order) misses the data points while the full order model (5^{th} order) matches the data points a little better. However, for the data points (after the first 5 data points) which are not used in the identification both the full as well as reduced order models predictions do not match with the validation data.

It is important to mention that in clinical applications personalized drug dose response models from as few number of clinical data as possible is desired due to time required for each measurement. In this application, 5 data points correspond to 5-week of data collection time from patients. Therefore, more data points are not used in the identification algorithm. Different than the patient-1, patient-10 dose-response data presents a more challenging case due the variation in EPO dosage which is not used in the identification process. As before, the first 5 data points were used in the l_1-robust identification algorithm to find the model. The reduced order model is kept same as the full order (5^{th} order). The model for patient-10 is given in (12) and model predictions are shown in Fig. 3.

$$G^{10}(z) = \frac{-11.27z^5-19.62z^4+0.603z^3+19.72z^2+9.727z+0.02638}{z^5+1.228z^4-0.4048z^3-1.235z^2-0.4871z-0.001785} \quad (12)$$

The model for patient number 21 is given in (13) and model prediction is shown in Fig. 4. The full order model is reduced to 3^{rd} order model for the patient-21 obtained by l_1 robust identification. This patient is more challenging as this patient's EPO data has zero values. It means that since Hb was higher than the desired range of 11-12 g/dl. Therefore, the patient was not given any medication between weeks 14 and 17 as well as between weeks 35-44. The responses for full and reduced order models deviate from actual patient data as the EPO dosage is increased.

$$G^{21}(z) = \frac{-19.29z^3 + 9.71z^2 + 11.01z - 21.73}{z^3 - 0.5203z^2 - 0.3719z + 0.7698} \quad (13)$$

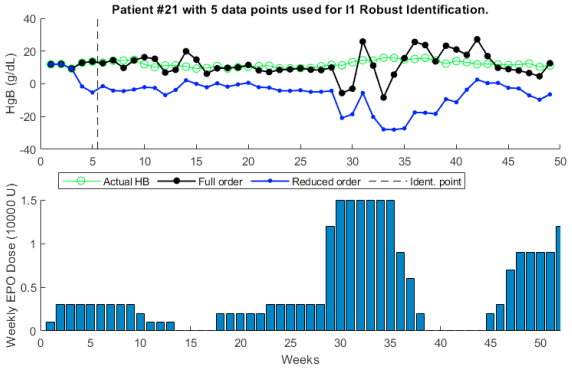

Fig. 4. Response of the patient-21 full and reduced order models obtained by the l_1 robust identification.

The model identification of patient 32 is a challenging task as the first 5 data points used for the identification of EPO data are zeros, but Hb values are not zero. The full order model for patient number 32 is reduced to 4^{th} order model. The model for patient number 32 is shown in (14) and model prediction is shown in Fig. 5.

$$G^{32}(z) = \frac{-8.27z^4-18.24z^3-27.81z^2-39.01z-49.78}{z^4+0.76z^3+0.5254z^2+0.3342z+0.1477} \quad (14)$$

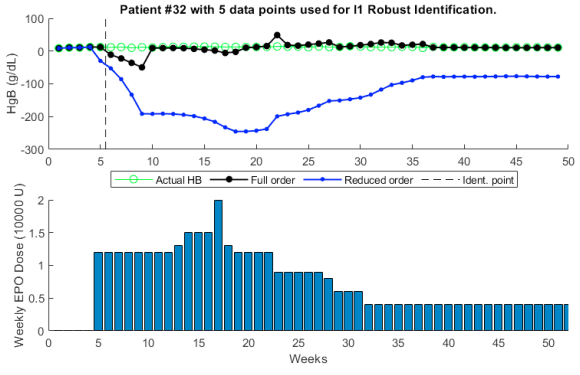

Fig. 5. Response of the patient-32 full and reduced order models obtained by the l_1 robust identification.

5.2 Semi-Blind Robust Identification Results

The above models found by l_1 robust identification assume the initial conditions equal to zero, which can highly affect the

identified model as for the patients of Chronic Kidney disease (CKD), the past medication affects the state of the patient. Thus, these effects are included in the model using the Semi-blind identification technique. For comparison purposes, the reduced-order models for both of the techniques are kept the same for the respective patient models. In figures of Semi-blind robust identification results, the red line with square markers shows the actual HB level of the patient, the solid blue line shows the model prediction results of full order model obtained using Semi-blind robust identification technique, the green line with diamond markers shows the prediction results of the reduced-order model identified by the Semi-blind robust identification, and the vertical dashed line shows the number of data points used in the identification process. The vertical blue bars shows the weekly EPO dosages. The model of patient number 1 obtained by the Semi-blind identification technique is given in (15) and model prediction results by one-step-ahead prediction are shown in Fig. 6:

$$G^1(z) = \frac{0.2022z^3 - 0.1034z^2 + 0.154z + 1.435^{-5}}{z^3 - 1.491z^2 + 1.263z - 0.7465} \quad (15)$$

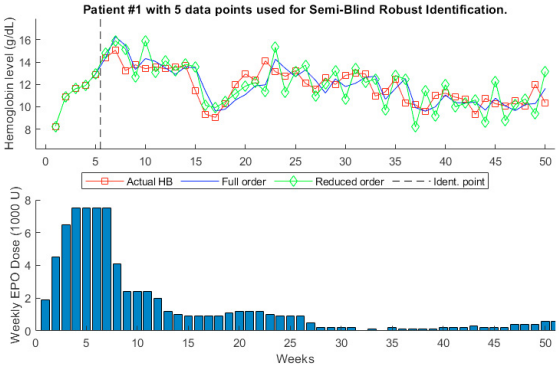

Fig. 6. Response of the patient-1 full and reduced order models obtained by the Semi-blind robust identification.

The MMSE analysis for the patient-1 shows less error for the Semi-blind robust identification as compared to the l_1 robust identification, as the Semi-blind robust identification technique accounts the effect of the initial conditions. These results show that previous medications used by the patients significantly affect the model identification. The system model for patient number 10 obtained by Semi-blind robust identification is given in (16) and model prediction is shown in Fig. 7:

$$G^{10}(z) = \frac{0.81z^5 - 0.62z^4 + 0.39z^3 - 0.23z^2 + 0.06z - 5.78\times10^{-5}}{z^5 - 1.75z^4 + 1.24z^3 - 0.76z^2 + 0.35z - 0.08} \quad (16)$$

The system model for patient number 21 obtained by Semi-blind robust identification and model prediction is shown in Fig. 8:

$$G^{21}(z) = \frac{0.86z^3 + 1.29z^2 + 0.81z + 9.122 \times 10^{-5}}{z^3 + 0.5283z^2 - 0.5356z - 0.9237} \quad (17)$$

The 3^{rd} order model response for the patient-21 shows good performance even there are a lot of variations in the EPO data of the patient, which is not being used in the identification process. The system model for patient number 32 obtained by Semi-blind robust identification and model prediction results are given in (18) and Fig. 9 respectively.

$$G^{32}(z) = \frac{0.79z^4 + 0.28z^3 - 0.44z^2 - 0.15z - 0.0016}{z^4 - 0.63z^3 - 0.90z^2 + 0.36z + 0.19} \quad (18)$$

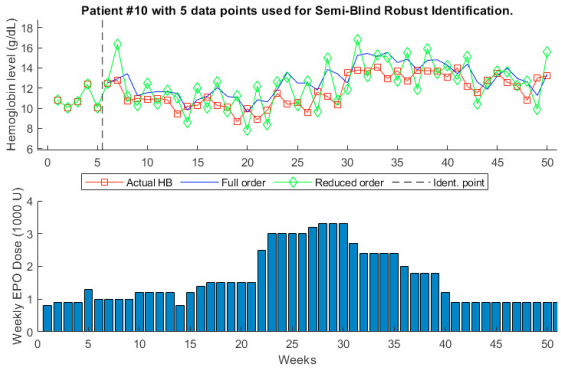

Fig. 7. Respons of the patient-10 full and reduced order models obtained by the Semi-blind robust identification.

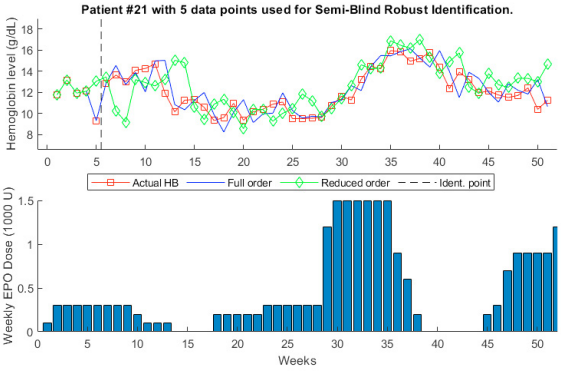

Fig. 8. Response of the patient-21 full and reduced order models obtained by the Semi-blind robust identification.

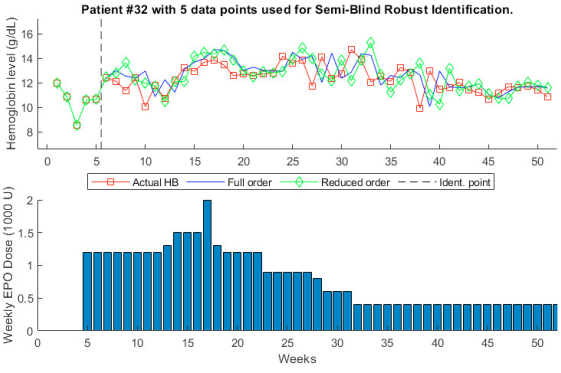

Fig. 9. Response of the patient-32 full and reduced order models obtained by the Semi-blind robust identification.

The reduced-order model for the patient-32 shows good performance, even the EPO data used in the identification process has zero values and after identification, the trend for EPO values is different. Table 1 shows the MMSE values of full and reduced-order models of respective patients obtained by both techniques. As it is seen in table 1 that Semi-blind robust identification technique provides better results as it includes the effect of the past effects of the medication.

6. CONCLUSION

In this research work, the individualized system models for patients of chronic kidney disease (CKD) is obtained to regulate

Table 1. MMSE analysis.

Method	Patient-1	Patient-10	Patient-21	Patient-32
Full order model				
l_1	275.36	195.324	47.93	219.8624
Semi-Blind	1.079	2.1308	1.2049	1.3252
Reduced order model				
l_1	2687	195.324	423.99	24496.03
Semi-Blind	1.89	6.51	3.03	1.38

the external human recombinant erythropoietin (EPO) dosage to maintain the hemoglobin (Hb) levels between 11 and 12 g/dL. The l_1 robust identification and Semi-blind identification techniques have been implemented on the clinical data set of fifty patients obtained from the University of Louisville, Kidney Disease program. The l_1 robust identification considers zero initial conditions. However, the Semi-blind identification technique takes into account the effects of initial conditions to obtain the patient model. Both of these techniques do not assume the probabilistic distribution of noise or predefined model structure. The obtained patient models are validated by using the one-step prediction method. The minimum mean square error (MMSE) is calculated for each patient between actual data and predicted data. The error in the model obtained in Semi-blind identification techniques is considerably less than l_1 robust identification technique. This research work provides a basis to obtain individualized models for new patients. The next phase is to design controllers for the patients based on the identified models and automate this procedure for new patients.

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