ROBUST IDENTIFICATION APPROACH TO INDIVIDUALIZED ANEMIA MODEL

Elom Akabua[1], Tamer Inanc[1], Adam Gaweda[2], Michael E. Brier[2,4], Seongho Kim[3] and Jacek M. Zurada[1]

[1] Department of Electrical Engineering, University of Louisville, Louisville, KY. 40292
(aeakab01, t.inanc, jacek.zurada)@louisville.edu

[2] Division of Nephrology, University of Louisville, Louisville, KY. 40292
adam.gaweda@louisville.edu

[3] Department of Bioinformatics and Biostatistics, University of Louisville, Louisville, KY. 40292
s0kim023@louisville.edu

[4] Department of Veteran Affairs, Louisville, KY. 40292
mebrie01@louisville.edu

Abstract

Over ninety percent of End Stage Renal Disease (ESRD) patients suffer from anemia due to insufficient endogenous production of human erythropoietin. Until the advent of Recombinant Human Erythropoietin (r-HuEPO) over 30 years ago, patients with ESRD were treated mainly with multiple blood transfusions. The high cost of r-HuEPO in addition to the narrow margin between an effective dosage and toxicity in drug administration calls for optimal dosage strategy capable of minimizing cost and toxicity while at the same time achieving the desired dosage outcome. It is well known from control theory that a controller can be designed for any plant provided there is readily available a valid model for such a plant. We present Robust Identification procedure, a dimensionality reduction technique capable of capturing the inherent dynamics of anemia patients; consequently producing individualized model suitable for robust control synthesis and any other controller design methodologies.

Keywords: hemoglobin, robust identification, Carathéodory-Fejér problem, erythropoeitin, anemia management

1 Introduction

Recombinant Human Erythropoietin (r-HuEPO) is currently the drug of choice for the treatment of patients with secondary anemia due to Chronic Kidney Disease (CKD) in periodic hemodialysis [11]. Prior to the mid 1980s, patients suffering from CKD were primarily treated by regular blood transfusions. The cumbersome process of blood transfusion and other health related complications associated with it called for an alternative method to ERSD therapy. By 1990, recombinant human erythropoietin (EPO) was developed and approved for such a purpose. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) has a recommended guideline to maintain hemoglobin level for anemics to be between 11 and 12 g/dL; however, there is no definitive strategy to achieve this range. As a result, several anemia management facilities developed their own Anemia Management Protocol (AMP), a dosing strategy often based on trial-and-error and prior experience. This approach often results to patient's hemoglobin level overshooting and undershooting the target range. In fact, it has been reported that only 38% of ESRD patients fall within the recommended range at a given time with AMP dosage strategy [6]. The high cost of EPO in addition to the narrow margin between an effective dosage and toxicity demands an optimal dosage strategy for ESRD therapy. In an effort to improve on the AMP, several attempts are made in the literature to stabilize erythropoiesis for ESRD patient ranging from a detailed physiological model to a simple black-box model (cf.[12], [14], [15], [2], [5], [1], [3], etc). Most of these approaches work well however, the obtained models are based on a use of large patient dataset. In cases where there was not sufficiently large dataset available, average population data were subsequently used. It is however well known that intra-individual variability makes it inappropriate to administer an "average" dosage to a patient and expect and "average" response. Thus none of these modeling procedures can be performed with small available patient dataset. Additionally, an assumption made is that the model obtained accurately represents the true system and there is no account for uncertainty in the model. Any discrepancy between system out and model output are attributed to noise in measurement. In Robust Control, we are interested in designing a controller to achieve certain design objectives provided we have available a nominal model as well as an uncertainty in the system that explains dynamics un-modeled by the nominal model of the system. By robust we imply a small change in input of the system should result to small change in the output of the system. For the case of individualized anemia management, this implies a small change in EPO dose should result in small change in hemoglobin level. This prevents an issue often encounter in drug dosing –thus small change in dosing strategy leading to huge change in patient response [3].

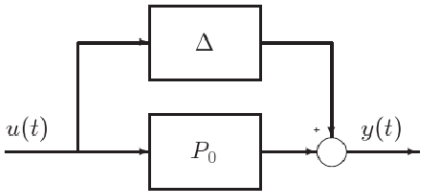

Figure 1. Robust Controller structure: Nominal and additive uncertainty.

The structure shown in figure 1 is a generic description of an additive uncertain Robust system model. In addition to the input-output, *(u(t), y(t))*, it also contains a nominal model P_0 as well as a additive unmodelled dynamic, Δ. The general equation representing the system is depicted in equation (1). Our main focus of this work is to obtain a nominal model, P_0, as well all the uncertainty bound Δ measured in l_1-norm suitable for robust control synthesis.

$$P(s) = P_0 + \Delta \tag{1}$$

In the modeling process, our assumption on the system is very minimal. It is assumed the system to be identified is a Linear Time Invariant (LTI) causal stable system belonging to a model class S with a maximum gain K, and a decay rate ρ. It is further assumed that measurements of the system is affected by an unknown-but-bounded noise ϵ belonging to a set N. The a posteriori information includes the obtained input-output dataset of our system. The goal of robust identification is to obtain both the nominal model as well as the uncertainty model using both the a priori (S;K;ρ;N) and a posteriori (input-output data). The derived model is in the framework suitable for robust control synthesis method in l_1. Our interest is to formulate and model individualized anemia management problem suitable for robust control.

The paper is organized as followed: in section II, we present some necessary notations. In section III we provide brief overview on Robust Identification, particularly on l_1 identification. Section IV presents the anemia management problem and provides a robust identification approach to the problem we present Anemia Management problem. We present the results in V. The paper ends with conclusion and future work in section VI.

2 Notation

The following notations are used in the paper. Let $\mathcal{H}_\infty$ denote space of complex functions with bounded analytic inside the unit disk, equipped

with the norm $||G(z)||_\infty \triangleq ess \sup_{|z|<1} \bar{\sigma}(G(z))$. We are also interested in space $\mathcal{H}_{\infty,\rho}$ of transfer matrices in $\mathcal{H}_\infty$ analytic continuous inside the disk with a radius $\rho > 1$, i.e., we are interested in the space of exponentially stable systems with a stability margin of $(\rho - 1)$ equipped with the norm $||G(z)||_\infty \triangleq \sup_{|z|<1} \bar{\sigma}(G(z))$. Let ℓ_1 denote space of absolutely summable sequences $h = \{h_i\}$ equipped with the norm $||h||_{\ell_1} \triangleq \sum_{i=0}^{\infty} |h_i| < \infty$. Also of interest is the ℓ_∞ space of bounded sequences $h = \{h_i\}$ equipped with the norm $||h||\ell_\infty \triangleq \sup_{i\geq 0} |h_i| < \infty$. Given a sequence $h \in \ell_1$, its z-transform is defined as $H(z)$[1] $= \sum_{i=0}^{\infty} h_i z^i$. For an LTI system, an operator G mapping input data to an output data can be represented either as a (rational) complex-valued transfer function:

$$G(z) \doteq \sum_{i=0}^{\infty} g_i z^i$$

or as a minimal state-space realization:

$$G \equiv \left(\begin{array}{c|c} A & B \\ \hline C & D \end{array}\right)$$

In addition, for stable system G, we denote $T_G : \ell^\infty[0,\infty) \to \ell^\infty[0,\infty)$ the Toeplitz matrix. An operator mapping input sequence, u to and output sequence y is represented as:

$$\begin{bmatrix} y_0 \\ y_1 \\ \vdots \\ y_{N-1} \end{bmatrix} = \underbrace{\begin{bmatrix} g_0 & 0 & \cdots & 0 \\ g_1 & g_0 & \cdots & 0 \\ \vdots & \ddots & \ddots & 0 \\ g_{N-1} & \cdots & g_1 & g_0 \end{bmatrix}}_{T_G} \begin{bmatrix} u_0 \\ u_1 \\ \vdots \\ u_{N-1} \end{bmatrix}$$

3 Robust Identification

A. Introduction

The importance of obtaining mathematical model from finite, partial, and corrupt system can be witness in various fields ranging from a simple economic system to a complex one such as physiological systems. Generally, certain informations are readily available or known or assumed on the dynamics nature of the system under consideration. For example, the designer

[1]Notice that this is the standard z-transform evaluated at 1/z. This adoption allows us to define stability in terms of analyticity on a disk (rather than the complement of a disk) while at the same time leaving the unit circle invariant [8]

might assume the system to be of a certain model order, obey certain noise characteristics affecting system measurements, input range, etc. This available knowledge is known as the system *a priori* information. The *a posteriori* information is referred to the measurement data obtained from the system. Two basic paradigms are available in the literature for deriving such a mathematical model: stochastic and deterministic approach. In the stochastic settings, the assumed *a priori* system information includes a predetermined system model order and a stochastic noise with known statistical properties affecting measurement outputs. The performance measure is usually determined based on least square error.

Assumptions on error in measurement should be the least of a concern to a designer. The notion that a complex system can be modeled with a prescribed model structure is unrealistic. For most systems, there is readily available sensor measurement noise bound and when such information is available and statistical assumptions maybe questionable, a *deterministic* approach to deriving a model is the sound alternative.

B. Robust Identification

Compared with the stochastic system identification methods, the *a priori* assumptions on deterministic robust identification are very minimal. There is no assumption made on the order of the system and no assumption on the noise affecting its measured outputs. It is assumed the system belongs to a particular *class* and its measurement noise is *unknown but bounded* (UBB) by a known value which is often available for most systems. The aim is to obtain a suitable nominal model as well as a "hard" uncertainty bound using the *a posteriori* information (experimental data) and the *a priori* information (see figure 2). Such a derived nominal model and its uncertainty bound are suitable for any controller design synthesis including adaptive control, predictive control, $\mathcal{H}_\infty$ control, ℓ_1 control, and more importantly, robust control.

Robust Identification problem is a worst-case control oriented identification process originally proposed in [8] as an alternative to the classical system identification process to obtain "hard" bound on model error suitable for robust control.The classical system identification procedures are not suitable for robust control since it assumes a fixed model structure and a stochastic noise. Robust Identification is based on deterministic worst-case with no prior assumption on the model order. It identifies a family of models in which the central is considered the nominal model and the radius is the uncertainty see figure 2. Unlike classical system identification procedure, the uncertainty in the model originates from two different sources:

- Measurement noise.
- Lack of knowledge of the system itself due to limited experimental information provided by the system.

Fig. 2: A circle with the center denoting the nominal model and its radius, Δ, denoting the uncertainty in the model. It is assumed the true system is within the circle.

Hence, the identification procedure does not only depend on the experimental data but also on the *a priori* class of system to be identified. The procedure identifies a nominal model from the given *a posteriori* data and provides a worst-case bound on the $\mathcal{H}_\infty$-norm of the system for the purpose of robust control design.

As inputs, the Robust Identification algorithm admits both *a priori* as well as *a posteriori* information. The *a priori* information involves all assumptions made on the system including the maximum gain,K, and the stability margin ϵ. A *a posteriori* information to the identification algorithm includes the measurement data and the bounded noise on measurements. When the available *a posteriori* data is a point frequency measurements, the $\mathcal{H}_\infty$ identification procedure is used (see [8], [13]); whereas, ℓ_1 identification procedure is used for time domain data (see [10], [13]). For the time domain data, we will assume the following *a priori* information on our system:

- The system to be identified belongs to a class $\mathcal{H}_\infty(K)$ i.e the set of exponentially stable system with a stability margin of (ρ-1), and a peak response to complex exponential inputs of K.

$$H(z) = \sum_{k=0}^{\infty} h(k) z^k \tag{2}$$

  where $H(z)$ is the standard z-transform evaluated at $\frac{1}{z}$. Hence, causal stable system $H(z)$ is analytic inside the unit circle.
- A bound ϵ_t of the measurement noise $\eta_t(k) \in \ell_\infty(\epsilon_t)$ [4].

Then the Robust Identification problem is stated as follow: given N time domain noisy data and some *a priori* information on the system of $y(k) = h(k) + \eta(k)$,k = 0,...,N-1, determine:

1) Whether the a *a priori* information is consistent with the *a posteriori* information ("consistency" problem).

2) If 1 is true, then determine such a model as well as worst case identification error ("interpolation" problem).

C. Solving the Consistency and Interpolation Problem

As mentioned above, the consistency problem determines if the *a priori* assumptions on the system is consistent with the *a posteriori* information of the system. The following result will be used to establish the consistency problems:

Problem *1:* [4] Given complex numbers c_i, $i = 0, 1, \ldots, n-1$, determine a function $h \in \bar{\mathcal{B}}\mathcal{H}_\infty$ such that

$$h(\lambda) = c_0 + c_1\lambda + \ldots + c_{n-1}\lambda^{n-1} + \lambda^n \hat{g}(\lambda), \tag{3}$$

where $\hat{g} \in \bar{\mathcal{B}}\mathcal{H}_\infty$.
In essence, we are to determine the first n Taylor series coefficients of the function $h(\lambda)$ evaluated at zeros corresponding to the given complex numbers, i.e.,

$$\frac{h^k(0)}{k!} = c_k, \quad k = 0, 1, 2, \ldots, n-1.$$

To solve the above problem, we use the following Interpolation Theorem suitable of solving time-domain robust identification problems:

Lemma *1:* [4] (Carathéodory-Fejér). *Given complex numbers* c_i, $i = 0, 1, \ldots, n-1$, *there exists a function* $h \in \bar{\mathcal{B}}\mathcal{H}_\infty$ *such that* (3) *is satisfied if and only if the following semi-definite equation in* (4) *holds*

$$\mathbf{I} - \mathbf{T}_c^H \mathbf{T}_c \geq 0 \tag{4}$$

where T_c *is the associated Toeplitz matrix corresponding to the sequence* $c = [c_0, c_1, c_2, \ldots, c_{n-1}]$.
For equality in equation (4), the function is unique and non-unique otherwise. When non-unique, an arbitrary parameterization function $f(\lambda) \in \bar{\mathcal{B}}\mathcal{H}_\infty$ is chosen such

$$h(\lambda) = \frac{g_{11}(\lambda)f(\lambda) + g_{12}(\lambda)}{g_{21}(\lambda)f(\lambda) + g_{22}(\lambda)} \tag{5}$$

It has been shown that the consistency problem reduces to a (convex) Linear Matrix Inequality (LMI) feasibility problem. Specifically, the *a posteriori* information is consistent with the *a priori* information if there exists a vector $\mathrm{h} = [h_0, h_1, ..., h_{N_t-1}]$ such that the following LMIs satisfied:

$$\begin{aligned} M_R(\mathbf{h}) &= \begin{bmatrix} R^{-2} & \frac{\mathcal{F}^T}{K} \\ \frac{\mathcal{F}}{K} & R^2 \end{bmatrix} > 0 \\ -\epsilon_t &< \mathcal{F}^{\mathcal{T}}\mathbf{u} - y^t < \epsilon_t \end{aligned} \tag{6}$$

where $R = \text{diag}[\ 1 \quad \rho \quad \rho^2 \quad \dots \quad \rho^{N_t-1}\ ]$ and

$$\begin{aligned} \mathcal{F} &= \begin{bmatrix} h_0 & h_1 & \dots & h_{N_t-1} \\ 0 & h_0 & \dots & h_{N_t-2} \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & h_0 \end{bmatrix} \\ \mathbf{y} &= [y_0, y_1, \dots, y_{N_t-1}]^T \\ \mathbf{u} &= [u_0, u_1, \dots, u_{N_t-1}]^T \end{aligned} \tag{7}$$

Once the consistency is established by solving equation 6, the set of all models consistent with the *a priori* assumption and *a posteriori* data can be parameterized as a Linear Fractional Transformation (LFT) with a free parameter $q(z) \in \mathcal{BH}_\infty$. The central/nominal model is then obtained by setting $q(z) = 0$ with order less than or equal to N_t. Minimal state-space representation of the system $G(z)$ can be represented as follow:

$$\begin{aligned} G(z) &= \left[\begin{array}{c|c} A_G & B_G \\ \hline C_G & D_G \end{array}\right] \\ A_G &= A - [C_-^T C_- + (A^T - I)M_R]^{-1} C_-^T C_- (A - I) \\ B_G &= -[(A^T - I)M_R + C_-^T C_-]^{-1} C_- \\ C_G &= C_+[(A^T - I)M_R + C_-^T C_-]^{-1} C_-^T C_- (A - I) - C_+(A - I) \\ D_G &= C_+[(A^T - I)M_R + C_-^T C_-]^{-1} C_-^T \end{aligned} \tag{8}$$

where

$$A = \begin{bmatrix} 0 & I_{N_t \times N_t} \\ 0 & 0 \end{bmatrix},\ C_- = \overbrace{[1 \quad 0 \quad \dots \quad 0]}^{N_t},\ C_+ = \frac{\mathbf{h}^T R}{K}$$

The worst case model error can be computed as follow:[7]

$$\|e\|_\infty \leq \sum_{k=0}^{N-1} \min \left\{ \epsilon \sum_{i=0}^{k} |w_i| . \frac{K}{\rho^k} \right\} + \frac{K}{\rho^{N-1}(\rho - 1)} \tag{9}$$

where w_i depends only on the known input signal, in the simplest case where $u = \delta$ then $w_0 = 1, w_i = 0, i \geq 1$.

4 Application to anemia management problem

The goal in anemia drug dosing is to maintain patient hemoglobin level to be within the target range of $11 - 12 \frac{g}{dL}$. Since the drug dosing process

is carried out in a closed loop setting, it is imperative to use a feedback control system to achieve this objective. The use of feedback control system requires a model capable of describing the dynamic relationship between input Erythropoietin and output Hemoglobin. Robust Identification procedure is used to derive such a model. The necessary requirements for Robust Identification procedure includes the *a priori* and *a posteriori* information on the system to be identified. As state above, the *a priori* information includes the maximum gain on the system in response to a unit input and the its stability margin. A process to determine the maximum gain parameter was given in section III. The stability margin was estimated based on the structure of patient data. It should be pointed out that the accurate of these parameter values do not affect the attainment of a model. Since these parameters are estimated due to engineering faith, we must validate the model using new (unseen) data.

Using robust identification for patient modeling has three added benefits:

- No assumption is made about the model order.
- Small data set can be used for the model estimation.
- No statistical assumptions are made on the system.

5 Results

Figure 3 shows results of the robust identification procedure for patient #3. Twenty-two input/output (Epo/Hb) data were used to derived the model. Equation (10) shows the a 4^{th} order system nominal model. It can be observed from figure 3 that the model is able to follow the dynamic behavior of the patient. For validation purposes, we use the model to predict the 23^{rd} onward hemoglobin level of the patient.

$$G_{nom(\#3)}(z) = \frac{M(z)}{N(z)} \tag{10}$$

where $M(z)$ and $N(z)$ are defined by equations in (11)

$$\begin{aligned} M(z) &= 0.001163z^4 + 2.503e-05z^3 - 0.0007622z^2 \\ &\quad +6.269e-05z + 0.0005985 \\ N(z) &= z^4 - 0.3014z^3 - 0.4388z^2 + 0.121z - 0.1114; \end{aligned} \tag{11}$$

Using the notations of $\mathcal{Z}$ transform, the model equation in (10) can be translated to equation in (12).

$$\begin{aligned} Hgb_{k+4} &= 0.3014Hgb_{k+3} + 0.4388Hgb_{k+2} - 0.121Hgb_{k+1} \\ &\quad +0.1114Hgb_k + 0.001163Epo_{k+4} + 2.503e-05Epo_{k+3} \\ &\quad -0.0007622Epo_{k+2} + 6.269e-05Epo_{k+1} + 0.0005985Epo_k \end{aligned} \tag{12}$$

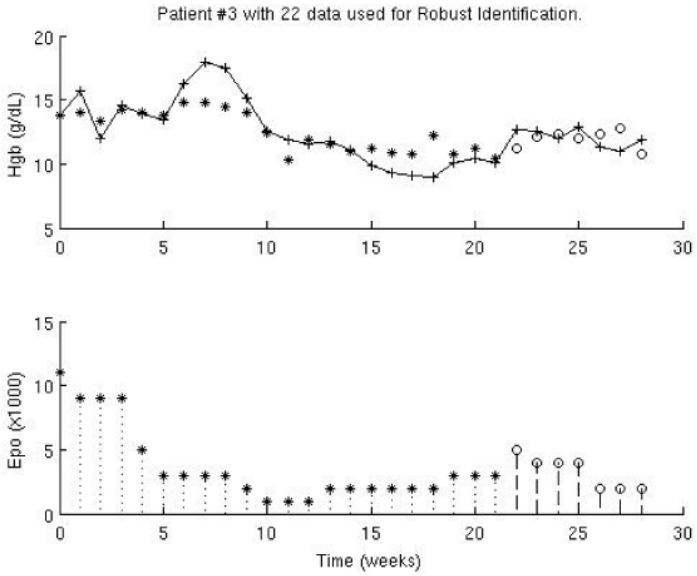

Fig. 3: Patient #3: [Top] 22 data points used for ℓ_1 identification (*). Prediction range (o). Reduced 4^{th} order model prediction output (+-). [Bottom] Input data used for ℓ_1 identification (*:) and data not used for identification (o-).

6 Conclusion

A robust identification methodology has been used to acquire ESRD patient model using actual patient data. The model obtained is a linear time invariant system model capable of extracting essential informations on patients dynamics. We further perform model validation to check for validity of our model using patient data not used in the identification process. It has been shown the procedure is capable of producing model suitable for Robust identification procedure. A merit of the procedure is its capabilities of generating a model with small dataset. The next step in this effort is to use the derived nominal model to design a controller for the patient.

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