Modeling of Hemoglobin Response to Erythropoietin Therapy through Constrained Optimization

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Abstract—Hemoglobin response modeling is critical for accurately predicting the hemoglobin level of anemic patients and it is the foundation of optimal control based Erythropoietin (EPO) therapy. In this paper, a novel Hemoglobin response modeling method is proposed. This method was inspired from a study on the physiological model of hemoglobin response to Erythropoietin. Insights on the effect of EPO is first gained from the physiological model and then transformed into an auto-regressive with exogenous input (ARX) model parameter pattern. The ARX model parameter estimation problem is formulated as a constrained optimization problem. Tests on simulated data using the physiological model and the real clinical data both show that the proposed modeling method has superior performance while also being less complex than the physiological model.

I. INTRODUCTION

Erythropoiesis is the process that produces red blood cells (RBCs). The primary function of RBCs is to transport oxygen from the lungs to other tissues as well as to transport carbon dioxide back to lungs for expulsion. Erythropoietin can stimulate the proliferation of RBC progenitors and is the major regulating agent of erythropoiesis. Due to insufficient endogenous production of erythropoietin, many End-Stage Renal Disease (ESRD) patients suffer from anemia. Anemia of ESRD patients can be treated by recombinant human erythropoietin (EPO). In practice, clinicians usually adjust the EPO dose amount and frequency based on the current hemoglobin (Hgb) measurements and dosing rules developed from retrospective studies. This process is labor intensive and requires trained personnel to assess monthly Hgb and iron levels and to make adjustments or assessments every 2 or 4 weeks. Furthermore, this one-size-fits-all protocol-based approach to anemia management with erythropoiesis-stimulating agents (ESAs) may result in undesired patterns of hemoglobin variability [1] and such outcomes are not optimal with respect to the cost of the EPO. It is therefore of great significance to develop decision supporting tools that can help the medical personnel on this difficult task and to reduce the treatment cost.

Recently, model based automatic controller design methods have gained popularity in this field [2] [3]. Many works have been done on the model construction of the relationship between Hgb and EPO. Currently available erythropoiesis models can be mainly categorized into two groups. One is physiologically driven models which include a group of differential equations deduced from process dynamic information. Historical data is then used to estimate the derived physiological parameters [4] [5]: The other group is data-driven modeling, which only uses the input and output data to get their interactive function via system identification techniques such as artificial neural networks or other regression models [6] [7]. Each kind of model construction method has its own benefits and drawbacks. Physiological models can grasp the main influencing factors of the whole process, however, it is difficult to model all of the process dynamics due to partially unknown features, simplified model structures, and the complexity of the entire process. On the other hand, data driven models only make use of the historical data and are often sensitive to process noise and they have limited generalization.

Considering the above existing problems, this paper seeks to explore a more effective data-driven modeling method for the erythropoiesis process. The proposed method is also data-driven, but with insights taken from the physiological model. The proposed model has similar structure to the classical ARX model. The difference is that the model parameters are enforced to have certain patterns learned from the physiological model. The whole modeling process is then transformed into a constrained optimization problem. Tests on simulated data and real clinical data both prove its effectiveness and efficiency.

The remaining part of the paper is arranged as follows. Section II introduces the physiological model for the erythropoiesis process and a study on the effect of EPO on the Hemoglobin response. Section III presents the proposed constrained data-driven modeling method. Section IV presents the test results, and the final conclusion is summarized in section V.

II. INSIGHTS FROM PHYSIOLOGICAL MODEL

A. Physiological model

Physiological modeling of the Hgb response includes pharmacokinetics (PK) and pharmacodynamics (PD). PK uses compartment models to describe how the drug is absorbed, distributed and eliminated through the body. PD model studies the conversion of drug concentrations at the pharmacologic site of action into biological effects, and describes how the drug interacts with the body.
For the Hgb response to EPO dosage, the PK model is described as
\[
dE(t) = -\frac{V \cdot E(t)}{K_m + E(t)} - \alpha \cdot E(t) + \text{dose}(t)
\]
(1)
\[
E_p(t) = E(t) + E_{en}
\]
(2)
\[
k_{in}(t) = \frac{S \cdot E_p(t)}{C + E_p(t)}
\]
(3)
\[
E_{en} = \frac{C \cdot H_{en}}{\mu \cdot K_H \cdot S - H_{en}}
\]
(4)

In the above equations, \(E(t)\) denotes the amount of exogenous recombinant human EPO in international unit (IU), \(E_{en}\) denotes the endogenous EPO, \(E_p(t)\) is the total EPO of the dynamic pool in plasma, \(k_{in}(t)\) is the RBC production rate, and \(\text{dose}(t)\) is the EPO dosing function which is modelled as a train of impulses. Model parameters include \(V, \alpha, S, K_m, C\), where \(V\) is the maximal clearance rate, \(\alpha\) is the linear clearance constant, \(S\) is the maximal RBC production rate stimulated by \(E_p\), \(K_m\) is the exogenous EPO level that produces half maximal clearance rate, and \(C\) denotes amount of \(E_p\) that produces half maximal production rate.

The PD part of the model describes the RBC dynamics (a detailed derivation is provided in the Appendix), which includes
\[
dR(t) = k_{in}(t - D) - \frac{4x_1(t)}{\mu^2}
\]
(5)
\[
dx_1(t) = x_2(t)
\]
(6)
\[
dx_2(t) = k_{in}(t - D) - \frac{4x_1(t)}{\mu^2} - \frac{4x_2(t)}{\mu}
\]
(7)
\[
Hgb(t) = K_H R(t)
\]
(8)

where \(R(t)\) is the RBC population, \(Hgb(t)\) is the hemoglobin level, and \(K_H\) is the mean corpuscular hemoglobin (MCH), which represents the average amount of Hemoglobin per RBC. \(D\) is the total time required for EPO-stimulated progenitor cells to progress through their various stages and finally become reticulocytes ready to mature into RBCs. \(\mu\) denotes the mean RBC life span, and \(H_{en}\) is the endogenous level of Hemoglobin due to \(E_{en}\). The initial conditions are given by
\[
R_0 = \frac{Hgb_0}{K_H}
\]
\[
x_{10} = \frac{\mu}{4K_H} (H_{en} - \mu \hat{R}_0)
\]
\[
x_{20} = \frac{1}{K_H} (K_H R_0 - H_{en} + \mu K_H \hat{R}_0)
\]

where \(Hgb_0\) and \(\hat{R}_0\) can be estimated from the data. The above model equations include a set of delayed differential equations (DDE), which represent the physiological model of Hemoglobin response to EPO dosage [4]. In this model, there are eight parameters \((\alpha, C, D, H_{en}, K_m, \mu, S, V)\) to be estimated.

B. EPO effect on Hemoglobin response

The above physiological model provides a basis for exploring the EPO effects on Hemoglobin response. The investigation step is as follows. First, the hemoglobin value is allowed to reach its steady state by adding an appropriate equal valued EPO dosing sequence which is found via repeated attempts using different dose amounts. Then, under this steady state, an impulse type of EPO input at different timing is applied to the physiological model to explore its effect on Hgb. The following calculation is performed to explore the effect of weekly historical EPO on hemoglobin (at day 500). First, the EPO dose from one week earlier, at day 493, is added individually and the current hemoglobin response at day 500 is recorded. This same procedure is then applied to an individual dose added two weeks prior, at day 486, and again the corresponding hemoglobin response at day 500 is recorded. This procedure continues in this fashion going back until day 1. Finally, EPO effect is calculated as the ratio of hemoglobin values and corresponding EPO doses administered at each dosing time. Two dosing amount scenario are investigated. In the first case, constant EPO dosage is applied. For the second case, unequal EPO doses is applied. In this way, many different cases with different parameters and different EPO sequence combinations have been studied. One example is shown in Fig. 1 and 2. In this example, parameters \(\alpha, C, D, H_{en}, K_m, \mu, S, V\) are set as 0.25, 22.45, 6.33, 7.9, 76.2, 92.2, 0.0084, 1655.13, respectively. In each figure, the red curve denotes the EPO effect, while the blue line represents the dosing amount for each impulse input.
III. PROPOSED MODELING APPROACH

A. ARX model structure

Autoregressive model with exogenous inputs (ARX) model is used for erythropoiesis modeling in [8]. An ARX model has the following form

\[ Hgb_t = a_0 Hgb_{t-1} + \sum_{k=1}^{K} b_k EPO_{t-k} \] (9)

where \( a_0, b_k \) are model coefficient parameters, \( Hgb_t \) denotes the \( t \)-th week hemoglobin value, \( EPO_{t-k} \) denotes the \( t-k \)-th weeks total EPO dose. \( K \) is the order of \( b_k \), which is set as 20 in this paper under the assumption that EPO dose made 20 weeks ago does not affect current Hgb level.

The above ARX model is a purely data-driven model. Its parameters \( a_0, b_k \) are completely dependent upon and estimated by the given training data. It can be shown that the ARX model identification results in estimated parameters exhibiting an irregular and highly random pattern for different patients. This is obviously inconsistent with the actual situation and our priori knowledge, which makes the ARX models physically uninterpretable.

On the other hand, according to the analysis in previous section, history EPO effect to current Hgb level exhibits a pattern: it first increases and reaches a peak, then gradually decreases. Thus, we propose to apply this type of pattern to the corresponding ARX model coefficients \( b_1, \ldots, b_K \). Based on this idea, a new data-driven model is developed with a similar structure as the ARX model, whose coefficients ought to have some patterns compatible with the EPO effect. Based on the above analysis, a different data-driven model is proposed for the Hgb response modeling. It is assumed that the coefficients \( b_1, \ldots, b_K \) have the following trend: before the peak time is reached, the coefficients are linearly increasing; while after the peak time, the coefficients are exponentially decreasing. The proposed ARX model structure is expressed as

\[ Hgb_t - Hgb_{base} = a_0(Hgb_{t-1} - Hgb_{base}) + \sum_{k=1}^{K} b_k(EPO_{t-k} - EPO_{base}) \] (10)

where \( Hgb_{base} \) denotes a steady state value of hemoglobin, and \( EPO_{base} \) is the corresponding steady state EPO dose. Both of the two parameters are unknown, and they are treated as variables to be optimized together with \( a_0, b_1, \ldots, b_K \).

B. Constrained optimization for parameter estimation

To estimate the parameters \( a_0, b_1, \ldots, b_K, Hgb_{base} \) and \( EPO_{base} \) in the model, a constrained optimization method is proposed. First, binary variables \( z_k \) are introduced to denote whether a time instance \( k \) is equal to or before the peak time (\( z_k = 1 \)) or after the peak time (\( z_k = 0 \)). The following constraint enforces this logic

\[-K z_k + 0.001 \leq k - t_{peak} \leq K(1 - z_k), k = 1, \ldots, K \] (11)

If time instance \( k \) is equal to or before the peak time (\( z_k = 1 \)), the constraint is reduced to \( k - t_{peak} \leq 0 \). If time instance \( k \) is after the peak time (\( z_k = 0 \)), the constraint is reduced to \( k - t_{peak} \geq 0.001 \).

The following constraints model the values of \( b_k \) before the peak time

\[-M(1 - z_k) \leq \alpha(k - 1) - b_k(t_{peak} - 1) \leq M(1 - z_k), \quad k = 1, \ldots, K \] (12)

If time instance \( k \) is equal to or before the peak time (\( z_k = 1 \)), the constraint is reduced to \( \alpha(k - 1) - b_k(t_{peak} - 1) = 0 \). This means a linear function is used to model the coefficient \( b_k = \alpha \frac{k - 1}{t_{peak} - 1} \). If time instance \( k \) is after the peak time (\( z_k = 1 \)), the constraint becomes redundant. Consider the magnitude of \( b_k \), \( M = 2 \) will be sufficiently large number.

The following constraints model the value of \( b_k \) after the peak time

\[-M \cdot z_k \leq \alpha e^{-\beta(k-t_{peak})} - b_k \leq M \cdot z_k, k = 1, \ldots, K \] (13)

If time instance \( k \) is after the peak time (\( z_k = 0 \)), the constraint is reduced to \( \alpha e^{-\beta(k-t_{peak})} - b_k = 0 \); that is an exponentially decaying function of time is used \( b_k = \alpha e^{-\beta(k-t_{peak})} \). If time instance \( k \) is equal to or before the peak time (\( z_k = 1 \)), the constraint becomes redundant.

The following constraint enforces that the model estimates reasonable Hemoglobin predictions,

\[ 7.0 \leq Hgb_t \leq 15.0, \forall t \] (14)

Finally, based on the analysis from ARX modeling, the following constraint is enforced

\[ 0.7 \leq a_0 < 0.99 \] (15)

Based on the pattern analysis of the effect of EPO doses on the Hemoglobin, the constraint \( b_1 = 0 \) is enforced. The peak time is allowed to vary within a flexible region and is enforced by the following constraint

\[ 1.0 \leq t_{peak} \leq 4.0 \] (16)

Parameter \( \alpha \) represents the peak effect of \( b_k \), and a lower bound of 0.1 is set on it. For parameter \( \beta \), a lower bound of 0.05 is set to control the decay rate of the \( b_k \) parameters after the peak period.

The objective function is the sum of squared error between the actual Hgb and the predicted Hgb.

\[ \min \sum_t (Hgb_t - Hgb_t^{actual})^2 \] (17)

The above optimization problem is a constrained mixed integer nonlinear optimization problem.

Example. To demonstrate the proposed constrained optimization approach for ARX model parameter estimation, a patient denoted as No. 25 is selected. The first 59 weeks of historical data was used for model training. The estimated parameters are \( a_0 = 0.7, EPO_{base} = 4 \times 10^{-8}, Hgb_{base} = 7.37, t_{peak} = 2.9 \) and the \( b_k \) parameters value are shown in Fig. 3.
It can be observed that the trained model output results in a good match with the actual data. In the mean time, the $b_k$ parameters satisfy the pattern learned from the physiological model. Notice that the $b_2$ value represents a point on the linear model before the peak time, while $b_3$ to $b_{20}$ follow the exponential decay function after the peak time.

To compare the performance of classical ARX modeling and the proposed constrained optimization based modeling method, a test on the simulated data with noise generated through physiological model is performed. The detailed procedure is described as follows: The eight parameters of physiological model are specified to simulate the process under a set of predefined EPO doses. With the simulated data, the first 50% is used to train the model and the remaining 50% of the data is used to validate the estimated model. The data is preprocessed by attaining hemoglobin values through linear interpolation and matching these values with EPO doses that include the sum of the current days’ EPO dose along with all the previous 6 days’ EPO doses lumped into one weekly dose. In this fashion, the data is re-sampled using 1 week intervals. The results in Fig. 4 and 5 show the results of the two ARX modeling methods on a simulated patient. Table I shows that the proposed method leads to an improved model validation performance as compared to the classical ARX modeling method.

<table>
<thead>
<tr>
<th></th>
<th>Mean RMSE</th>
<th>Std RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Training</td>
<td>Validation</td>
</tr>
<tr>
<td>Classical ARX</td>
<td>0.3411</td>
<td>1.1616</td>
</tr>
<tr>
<td>Constrained ARX</td>
<td>0.3632</td>
<td>0.6417</td>
</tr>
</tbody>
</table>

### IV. APPLICATION TO CLINICAL DATA

A set of clinical data obtained from 168 patients undergoing hemodialysis was studied. General statistics of the original data is shown in Table II. Next, the proposed method is compared with the physiological modeling method and the classical ARX modeling method.
TABLE II
CLINICAL DATA STATISTICS

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>168</td>
</tr>
<tr>
<td>Hgb (Mean ± Std)</td>
<td>10.4796 ± 0.5743</td>
</tr>
<tr>
<td>EPO dose (IU/week) (Mean ± Std)</td>
<td>3167.2 ± 2484.4</td>
</tr>
<tr>
<td>Hgb measurement frequency (average)</td>
<td>once every two weeks</td>
</tr>
</tbody>
</table>

Fig. 7. Classical ARX modeling based on clinical data of a test patient

validation results for one of the patients. The top plot of this figure denotes the EPO dosage information, the bottom one is the results of physiological model (the black curve represents the actual data, and the red curve is the predicted hemoglobin estimated by the physiological model in which the first 50% of the figure is the training curve, and the remaining 50% is the validation curve). It is seen from Fig. 6 that in most cases the physiological model can capture the main variation of Hgb value. However, this physiological model parameter estimation is time-consuming since it involves several iterations of a DDE simulation.

B. Classical ARX modeling

Hgb and EPO doses from the clinical data are used to estimate the classical ARX models in this test. Weekly data points for EPO and Hgb are first calculated in which the weekly Hgb values are obtained via linear interpolation and the corresponding weekly EPO doses are obtained by summing the current day’s EPO dose along with the 6 previous day’s EPO doses. The ARX model is trained and validated using the Matlab functions arx.m and predict.m, in which the training and validation ratio is set to 50%, the input delay is set as 1, the order of polynomial a and b is set as 1 and 20 respectively, and its prediction horizon is chosen as infinite.

Partial ARX model prediction results on real data are given in Fig. 7, which includes three curves, where the top curve is the EPO sequence with respect to each week, the middle figure is the training (the first 50%) and prediction results (the remaining 50%) (the black curve denotes the real data while the red curve denotes the ARX model results), and the bottom figure denotes the coefficients values of $b_1, \cdots, b_K$.

Fig. 8. Constrained ARX modeling based on clinical data of a test patient

It can be seen from Fig. 7 that the ARX models’ training accuracy is good, but its generalization ability is not satisfactory; the bottom curve shows that the $b_k$ coefficients follow a random pattern, which has no obvious physical meaning.

C. Constrained ARX modeling

Next, the proposed constrained ARX modeling method is tested. Weekly data points for EPO and Hgb are calculated in the same manner as the classical ARX modeling method. The proposed model is trained and validated using both Matlab and GAMS together. Training and validation data are produced in Matlab, and the model estimation is performed using the MINLP solver DICOPT in GAMS [9]. In this method, the training and validation ratio is again 50%, the number of b coefficients is set as 20 which is the same number as that in the ARX model, and an infinite prediction horizon is chosen. A patient’s results are shown in Fig. 8. This method was tested on other patients and produced similar results to those shown here.

It can be seen from Fig. 8 that compared to the classical ARX model, the proposed modeling method has better generalization ability; compared to the physiological model, it has better accuracy in training and validation; and it coefficients $b_1, \cdots, b_K$ represent some general pattern which has some interpretable meaning.

D. Comparison

A comparison of the performance of the above three modeling techniques are given in Table III, which lists the mean and standard deviation of the root-mean-square error (RMSE) over all patients. It is observed that the proposed model has the least training error and prediction error among the three types of models on the real clinical data in most cases.

V. CONCLUSIONS

This paper proposes a novel method for Hemoglobin response modeling. The proposed approach was statistically validated on simulated data and clinical data. Compared to physiological model, the proposed model has simpler structure and comparable performance; while compared to
TABLE III
STATISTICAL RESULTS ON CLINICAL DATA

<table>
<thead>
<tr>
<th></th>
<th>Mean RMSE</th>
<th>Std RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training</td>
<td>0.9831</td>
<td>1.3083</td>
</tr>
<tr>
<td>Validation</td>
<td>0.4068</td>
<td>0.6727</td>
</tr>
</tbody>
</table>

**APPENDIX**

The number of red blood cells $R$ in the pool is determined by the production rate $k_{in}(t)$ and the loss rate $k_{out}(t)$. This can be modeled as

$$\frac{dR}{dt} = k_{in} - k_{out} \quad (A.1)$$

Assuming that a cell exits the pool at the end of its lifespan (i.e., the cell dies), the loss rate can be calculated based on the cell lifespan distribution. Assuming the probability density function of its lifespan is $l(\tau)$ with $0 < \tau < \infty$, then

$$k_{out}(t) = \int_{0}^{\infty} k_{in}(t-\tau)l(\tau)d\tau = k_{in} * l \quad (A.2)$$

Notice that the above integration represents a convolution. Then Equation A.1 becomes

$$\frac{dR}{dt} = k_{in} - k_{in} * l \quad (A.3)$$

A reasonable assumption is that the probability density function of the life span follows a gamma distribution with $\tau_0$ being half of the mean life span (i.e., $\tau_0 = \mu/2$). Consider the following density functions:

$$l_1(\tau) = \frac{1}{\tau_0} e^{-\tau/\tau_0}, l_2(\tau) = \frac{1}{\tau_0} \tau e^{-\tau/\tau_0}, l_3(\tau) = \frac{1}{2\tau_0^2} \tau^2 e^{-\tau/\tau_0}$$

Their derivatives have the following relationships:

$$l'_1 = -\frac{1}{\tau_0} l_1, l'_2 = \frac{1}{\tau_0} (l_1 - l_2), l'_3 = \frac{1}{\tau_0} (l_2 - l_3)$$

Furthermore, assuming the probability density function of the lifespan distribution is $l_2$, then Equation A.3 becomes

$$\frac{dR}{dt} = k_{in} - k_{in} * l_2 \quad (A.4)$$

Define a new variable $x_1 = \frac{\tau^2}{\tau_0} (k_{in} * l_2)$, then Equation A.4 becomes

$$\frac{dx_1}{dt} = k_{in} - \frac{x_1}{\tau_0} \quad (A.5)$$

or

$$\frac{dR}{dt} = k_{in} - \frac{4x_1}{\mu^2} \quad (A.6)$$

Define $x_2 = \tau_0 (k_{in} * l_1) - \tau_0 (k_{in} * l_2)$, then it is easy to prove

$$\frac{dx_1}{dt} = x_2 \quad (A.7)$$

and

$$\frac{dx_2}{dt} = k_{in} - \frac{4x_1}{\mu^2} - \frac{4x_2}{\mu} \quad (A.8)$$

Equations A.6, A.7 and A.8 represent the PD model of the Hemoglobin response. Finally, considering the time delay for EPO-stimulated progenitor cells to mature into RBCs, a time delay $D$ can be added to the $k_{in}$ term.

**REFERENCES**