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Individualized Drug Dosing using RBF-Galerkin Method: Case of Anemia Management in Chronic Kidney Disease

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Abstract

Background and Objective: Anemia is a common comorbidity in patients with chronic kidney disease (CKD) and is frequently associated with decreased physical component of quality of life, as well as adverse cardiovascular events. Current treatment methods for renal anemia are mostly population-based approaches treating individual patients with a one-size-fits-all model. However, FDA recommendations stipulate individualized anemia treatment with precise control of the hemoglobin concentration and minimal drug utilization. In accordance with these recommendations, this work presents an individualized drug dosing approach to anemia management by leveraging the theory of optimal control.

Methods: A Multiple Receding Horizon Control (MRHC) approach based on the RBF-Galerkin optimization method is proposed for individualized anemia management in CKD patients. Recently developed by the authors, the RBF-Galerkin method uses the radial basis function approximation along with Galerkin error projection to solve constrained optimal control problems numerically. The proposed approach is applied to generate optimal dosing recommendations for individual patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Results: Performance of the proposed approach (MRHC) is compared in silico to that of a population-based anemia management protocol and an individualized multiple model predictive control method for two case scenarios: hemoglobin measurement with and without observational errors. In silico comparison indicates that hemoglobin concentration with MRHC method has less variation among the methods, especially in presence of measurement errors. In addition, the average achieved hemoglobin level from the MRHC is significantly closer to the target hemoglobin than that of the other two methods, according to the ANOVA statistical test. Furthermore, drug dosages recommended by the MRHC are more stable and accurate, also reach the steady-state value notably faster than those generated by the other two methods.

Conclusions: The proposed method is highly efficient for the control of hemoglobin level, yet provides accurate dosage adjustments, in the treatment of CKD anemia.

Keywords

Anemia management; optimal control; individualized drug dosing; RBF-Galerkin method

I. INTRODUCTION

Erythropoietin (EPO) is a glycoprotein hormone produced by kidney promoting the formation of red blood cells (RBCs) in bone marrow. Decreased EPO production in Chronic Kidney Disease (CKD) results in anemia, a condition which mainly affects the physical component of health-related quality of life (QoL), but is also associated with increased risk of cardiovascular events, and even mortality [1]. Discovery of exogenous recombinant human EPO in the late 1980s has revolutionized the treatment of CKD-related anemia [2]-[5], which until that point was primarily treated by repeated blood transfusion– a procedure associated with several complications, including increased risk of infections, allergic reactions, and sensitization impeding kidney transplantation [6]-[8]. The EPO dose adjustments in CKD patients have always been performed to achieve hemoglobin (Hb) concentration within a target range, specified by national guidelines [1].

The FDA-approved product information for the EPO stipulates dose individualization and using minimum necessary dose of the drug to achieve the target Hb [9]. The time delayed effect of EPO and relatively slow dynamics, related to red cell turnover, as well as large inter-individual variability in response to EPO make dose individualization a challenge to physicians. Traditional expert rule-based dose adjustment protocols are associated with EPO doses larger than necessary and increased Hb fluctuations. These phenomena have been linked to increased risk of serious cardiovascular problems and thrombotic events [10], [11]. Automatic control techniques for EPO dose individualization would therefore be of great importance to make the anemia treatment more efficient [12]-[18]. Most of the existing techniques however [12]-[16] are population-based and treat individual patients with a one-size-fits-all model [19]. The large inter-individual variability in response to EPO demands more precise *individual-based* control approaches [20]. Recent studies have shown that individualization of EPO dosing decreases the drug utilization, also stabilizes Hb concentration and hence reduces the need for blood transfusions [9], [18]. In [17], a support vector regression approach along with a multilayer perceptron neural network was applied to develop a system for personalized anemia management. However, this approach was strictly

focused on predicting the optimal EPO dose directly from treatment data, rather than designing an optimal controller around an individualized dose-response model [21]. Along the lines of traditional control design, a model predictive control (MPC) approach was successfully applied to anemia management problem, first based on a population-dose-response model [14], [15] and subsequently as an individualized method using multiple MPC controllers [18]. The multiple MPC-driven anemia management resulted in promising outcomes such as reduced Hb variability, decreased EPO utilization when compared to national average, and reduced need for blood transfusions [18]. However, through computer simulation, the method was found to be suboptimal in terms of time to achieve target Hb among patients with low rate of response to EPO. Also, as shown later in Section V, around 5% random error, which is not unlikely in practice considering measurement errors as well as other factors that are not included in a patient model, can make the EPO dosing recommended by the approach of [18] fluctuating and quite unreliable. Moreover, the weekly dose of the EPO can be greatly improved using a more accurate optimal control solution such as [22]. In our previous work [22]-[24], we demonstrated superior performance of a radial basis function (RBF)-based optimal control method for guiding the EPO dose adjustment, compared to a standard population-based clinical protocol commonly used in dialysis facilities. However, the Hb observational errors have not been included in our previous design which can dramatically affect the stability and robustness of the approach. Also, the results of the RBF method were not compared with other individualized approaches such as the method presented in [18].

In this work, we propose a new approach, called the RBF-Galerkin method, for the EPO dosing problem and design a multiple receding horizon control (MRHC) approach based on the RBF-Galerkin method for individualized anemia management. RBF-Galerkin method has been recently developed by Mirinejad et al. [25] to provide a flexible, efficient RBF framework for solving general optimal control problems. The method provides a highly accurate numerical solution to constrained optimal control problems, so it is applied as a means to find the individualized weekly dose of the anemia drug for CKD patients. Performance of our proposed approach is compared in silico to that of a population-based anemia management protocol (AMP) [1] and the individualized approach presented in [18] for two case scenarios: Hb measurement with and without observational errors. The outcome of this work is twofold: first, by finding the individualized EPO dosages necessary for achieving a desired Hb, the side effects of drug overdose are minimized. In addition, considering the cost of medication, minimizing the EPO dose can reduce its usage, and hence results in potential saving for health care costs, which could be another benefit of the current work. The paper is organized as follows: the anemia management problem is introduced first, followed by definition of the optimal control problem in Section II. Section III explains the MRHC approach based on the RBFGalerkin optimization method for anemia management. Section IV presents the in silico results, followed by the interpretation of results in Section V. Statistical comparison between our proposed method and two other approaches for anemia management are discussed in Section VI, and finally, conclusions presented in Section VII summarize the paper.

II. Anemia Management Problem

A. Introduction and Definition

Healthy kidneys produce EPO prompting bone marrow to make RBCs. As a consequence of kidney failure, patients with CKD are at increased risk of developing anemia. This comorbidity is typically associated with extreme weakness, tiredness, dizziness, and diminished cognitive abilities, leading to decreased QoL for CKD patients. One of the treatment options for CKD-related anemia is the administration of exogenous EPO. The weekly dose of this drug is typically determined based on the patient's Hb level and its variation, which should be maintained within target ranges recommended by national guidelines [1]. To achieve this goal, dialysis organizations often use their own proprietary anemia management protocols (AMP). An AMP is a rule-based expert system which guides EPO dose titrations based on Hb and/or its rate of change [1]. Commonly these rules are derived by a human expert based on observations and experience acquired within a population of patients. As a result, they do not take into account individual patient's dose-response profile and may ultimately lead to suboptimal results in individual patients [18], [19]. To address this challenge, modern control techniques could be used to perform more nuanced dosing adjustments tailored to individual patient's characteristics, while accounting for uncertainty inherently present in clinical data [9], [18]. Such techniques could provide more precise dose control and outperform the standard AMPs [14], [15], [18], [23], [24].

B. Individualized Drug Dosing as an Optimal Control Problem

Hb measurement and EPO dose for 56 CKD patients on dialysis were collected from the University of Louisville Kidney Disease Program. Patient data contain Hb level (weekly) and EPO dose (given 1 to 3 times per week), over 52 weeks. The data collection was conformed to the Declaration of Helsinki and approved by the University of Louisville Institutional Review Board. Six patients in the study cohort were eliminated from analysis due to insufficient data. Firstorderto third-order models were developed for each patient using the system identification toolbox in MATLAB. Since there were no meaningful change from the second to third order models, the second-order model was chosen for each patient, which is consistent with other previously developed pharmacodynamic models of erythropoiesis [12], [21]. To simulate the anemia treatment in silico, a second-order repeated pole dose-response model depending on unknown individual parameters covering wide range of patient types (good, average, through poor responders) was used. The transfer function of this model can be written as

$$G(s) = Y(s)/U(s) = k/(\tau s + 1)^2 . \quad (1)$$

where $Y(s)$ and $U(s)$ are Hb concentration (output) and EPO dose (input), respectively. The parameter k describes patient's responsiveness to EPO and could vary in the range of 0.2–1 g/dL/1,000 U. High values of k imply the good response, while low values indicate the poor response (resistance). The parameter τ is the time constant, related to the RBC lifespan, and assumed to vary in the range of 60–120 days, which is consistent with the published clinical data [26], [27]. The following assumptions are also being made. Baseline hemoglobin (Hb_0),

the patient's Hb concentration before starting the EPO treatment, is assumed to be in the range of 7–9 g/dL. The desired hemoglobin (Hb_T) range is 10–12 g/dL [1]. The maximum permissible EPO dose is set to 20,000 U per week and the EPO dose adjustment limited to not more than 50% of its steady state value. Furthermore, the Hb rate of change is limited to ±0.05 g/dL. Using the state space model for the transfer function of (1) and considering the aforementioned assumptions, we represent anemia management in the format of an optimal control problem as to minimize the performance index

$$J = \int_0^{t_f} \left(y_1(t) - Hb_T\right)^2 + \left(u(t) - u_{ess}\right)^2 dt \rightarrow \ general\ form \quad J = \int_0^{t_f} (x(t), u(t))dt \qquad (2)$$

subject to state dynamics,

$$\dot{\mathbf{x}}(t) = \begin{bmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \end{bmatrix} = \begin{bmatrix} -(2/\tau)x_1(t) - \left(1/\tau^2\right)x_2(t) + \left(k/\tau^2\right)u(t) \\ x_1(t) \end{bmatrix} \rightarrow \ general\ form \ \ \dot{x}(t) = f(x(t), u(t)$$

)

(3)

mixed state-control path constraints,

$$\left.\begin{array}{l} 0 \le u(t) \le 20,000 \\ \left|\dot{u}(t)\right| \le 0.5u_{ess} \\ \left|x_1(t)\right| \le 0.05 \end{array}\right\} \rightarrow \ general\ form\colon q(x(t), u(t)) \le 0 \qquad (4)$$

and boundary conditions,

$$\mathbf{x}(0) = \begin{bmatrix} x_1(0) \\ x_2(0) \end{bmatrix} = 0 \rightarrow \ general\ form\colon \gamma\left(\mathbf{x}(0), \mathbf{x}\left(t_f\right)\right) = 0 \qquad (5)$$

where the outputs $\mathbf{y}(t) = [y_1(t)\ y_2(t)]^T = [x_2(t) + Hb_0\ \ x_1(t)]^T$, and $u(t)$, $\dot{u}(t)$, $y_1(t)$, and $y_2(t)$ denote EPO dose, its derivative, Hb level, and its derivative, respectively. Also, $x_1(t)$ and $x_2(t)$ are states of the system and u_{ess} is the steady-state value of the EPO calculated from (1) for each individual, i.e. $u_{ess} = (Hb_T - Hb_0) / k$. To convert the dosing problem to a more flexible formulation, we have also shown a general form that may include nonlinear equations for state dynamics, path constraints and boundary conditions, if those equations need to get updated based on the physician's assessment or updated patient model.

III. RBF-Galerkin Method for Individualized Anemia Management

In this section, we briefly introduce an RBF-Galerkin solution to the drug dosing optimal control problem of (2)–(5) and then design an MRHC approach based on the RBF-Galerkin method for individualized anemia management.

A. RBF-Galerkin Solution

A direct method based on RBF parameterization, arbitrary discretization, Galerkin projection, and nonlinear programming (NLP) is proposed to solve the optimal control problem of (2)–(5) numerically.

RBF Definition: RBF is a real-valued function whose value depends only on the distance from a fixed point, called center [28],

$$\rho(\mathbf{y}, c) = \rho(\|y - c\|) \quad (6)$$

where ρ is the RBF,$\| \|$ is the Euclidean norm, and $\boldsymbol{c}$ is the RBF center. Any function satisfying (6) is called an RBF function. In general, an RBF could be piecewise smooth like Polyharmonic Splines or infinitely smooth (global RBF) such as Gaussian (GA) RBFs or Multiquadrics (MQ) [28].

In the RBF-Galerkin method, global RBFs are used as the trial functions for approximating the optimal control problem. For brevity and without loss of generality, same type of RBFs, ρ, and same number of RBFs, N, are assumed to be used for the approximation of state $\boldsymbol{x}(t) = [x_1(t)\ x_2(t)]^T$ and control $u(t)$ as

$$\mathbf{x}(t) \approx \mathbf{x}^R(t) = \sum_{i=1}^{N} \boldsymbol{\alpha}_i \rho\left(\left\|t - t_i\right\|\right) = \sum_{i=1}^{N} \boldsymbol{\alpha}_i \rho_i(t) \quad (7)$$

$$u(t) \approx u^R(t) = \sum_{i=1}^{N} \beta_i \rho\left(\left\|t - t_i\right\|\right) = \sum_{i=1}^{N} \beta_i \rho_i(t) \quad (8)$$

where $\boldsymbol{x}^R(t)$, $u^R(t)$ denote the RBF approximation of $\boldsymbol{x}(t)$, $u(t)$, respectively. Also, $\rho_i(t)$ is the RBF, and $\boldsymbol{\alpha}_i$, β_i are RBF weights for $\boldsymbol{x}^R(t)$, $u^R(t)$, respectively. Taking derivative of (7) with respect to t yields

$$\dot{\mathbf{x}}(t) \approx \dot{\mathbf{x}}^R(t) = \sum_{i=1}^{N} \boldsymbol{\alpha}_i \dot{\rho}\left(\left\|t - t_i\right\|\right) = \sum_{i=1}^{N} \boldsymbol{\alpha}_i \dot{\rho}_i(t) \quad (9)$$

Substituting (9) in (3), the *defect constraints* (residuals) $\boldsymbol{\psi}(t)$ are defined as

$$\psi(t) = \mathbf{f}\left(\boldsymbol{\alpha}_i, \beta_i, \rho_i(t)\right) - \sum_{i=1}^{N} \boldsymbol{\alpha}_i \dot{\rho}_i(t). \quad (10)$$

A Galerkin projection [29] is applied to defect constraints in which the defect constraints are set to be orthogonal to every member of the RBF basis functions, i.e.

$$\int_0^{t_t} \boldsymbol{\psi}(t)\rho_j(t)\,\mathrm{d}t = \mathbf{0} \;\; for\; j = 1, 2, \ldots, N \quad (11)$$

where $\rho_j(t)$ is the RBF. It implies that the defect $\boldsymbol{\psi}$ converges to zero in the mean (in the limit $N \to \infty$). If $\{\boldsymbol{x}^R, \boldsymbol{u}^R\}$ satisfies the initial conditions of (3), and $\boldsymbol{\psi}$ converges to zero in the mean, the approximated solution of (3), $\{\boldsymbol{x}^R, \boldsymbol{u}^R\}$, converges to its exact solution, $\{\boldsymbol{x}, \boldsymbol{u}\}$, in the mean, i.e.

$$\lim_{N \to \infty} \left\| \left\{\mathbf{x}^R, \mathbf{u}^R\right\} - \{\mathbf{x}, \mathbf{u}\} \right\|_2 = 0. \quad (12)$$

In other words, by applying the Galerkin error projection, the defect constraints are minimized in L^2 -norm sense. Now, substituting (10) in (11) and approximating the integral of (11) by a proper quadrature yields

$$\sum_{k=1}^{N} w_k \left(\mathbf{f}\left(\boldsymbol{\alpha}_i, \beta_i, \rho_i(t_k)\right) - \sum_{i=1}^{N} \boldsymbol{\alpha}_i \dot{\rho}_i(t_k) \right) \rho_j(t_k) = \mathbf{0} \quad (13)$$

for $j = 1, \ldots, N$, where w_k, $k = 1, 2, \ldots, N$ are quadrature weights corresponding to the type of quadrature points used for approximating the integral.

A non-negative slack variable function $\boldsymbol{p}(t)$ is defined to convert the inequality constraints of (4) to equality constraints and approximated using N global RBFs as:

$$\mathbf{p}(t) \approx \mathbf{p}^R(t) = \sum_{i=1}^{N} \boldsymbol{\kappa}_i \rho\left(\left\| t - t_i \right\|\right) = \sum_{i=1}^{N} \boldsymbol{\kappa}_i \rho_i(t) \quad (14)$$

where $\boldsymbol{p}^R$(t) is the RBF approximation of $\boldsymbol{p}(t)$ and $\boldsymbol{\kappa}_i$ denote RBF weights for the $\boldsymbol{p}^R(t)$. The residual of path constraints, $\boldsymbol{R}_q$, is calculated as

$$R_q = q(\boldsymbol{\alpha}_i, \beta_i, \rho_i(t)) + \sum_{i=1}^{N} \boldsymbol{\kappa}_i \rho_i(t). \quad (15)$$

Similar to (11), a Galerkin projection is applied to the residual $\boldsymbol{R}_q$ to set it orthogonal to every member of the RBFs which can be shown in the discretized form as

$$\sum_{k=1}^{N} w_k \left(q(\alpha_i, \beta_i, \rho_i(t_k)) + \sum_{i=1}^{N} \kappa_i \rho_i(t_k) \right) \rho_j(t_k) = 0 \quad (16)$$

for $j = 1,\ldots, N$, where w_k are similar quadrature weights as used in (13). Using the similar quadrature scheme for the approximation of performance index, J, the optimal control problem of (2)–(5) is eventually transcribed into the following NLP problem:

Determine $\boldsymbol{A} = (\boldsymbol{\alpha}_1\ \boldsymbol{\alpha}_2\ \ldots\ \boldsymbol{\alpha}_N)^T{}_{N\times 2}$, $B = (\beta_1\ \beta_2\ \ldots\ \beta_N)^T{}_{N\times 1}$, $\boldsymbol{k} = (\boldsymbol{\kappa}_1, \boldsymbol{\kappa}_2, \ldots, \boldsymbol{\kappa}_N)^T{}_{N\times q}$, and possibly final optimization time that minimize the performance index

$$J = \sum_{k=1}^{N} w_k L(\boldsymbol{\alpha}_i, \beta_i, \rho_i(t_k)) \quad (17)$$

subject to:

$$\sum_{k=1}^{N} w_k \left(\mathbf{f}(\boldsymbol{\alpha}_i, \beta_i, \rho_i(t_k)) - \sum_{i=1}^{N} \boldsymbol{\alpha}_i \dot{\rho}_i(t_k) \right) \rho_j(t_k) = 0 \quad (18)$$

$$\boldsymbol{\gamma}\left(\boldsymbol{\alpha}_i, \rho_i(0), \rho_i(t_f)\right) = 0$$

$$\sum_{k=1}^{N} w_k \left(\mathbf{q}(\boldsymbol{\alpha}_i, \beta_i, \rho_i(t_k)) + \sum_{i=1}^{N} \boldsymbol{\kappa}_i \rho_i(t_k) \right) \rho_j(t_k) = 0$$

for $j = 1,2,\ldots, N$. The proposed approach is called the RBF-Galerkin solution to the EPO dosing optimal control problem of (2)–(5). Please note that in general, the problem described by (17) and (18) is an NLP problem, but it could be specifically reduced to a linear programing problem considering those certain linear constraints represented in (3)–(5). The resulted NLP can be efficiently solved by well-developed NLP solvers available. For this work, SNOPT [30], a sparse solver, was chosen to solve the NLP problem described by (17) and (18).

Since the RBF interpolation for global RBFs is always unique [28], regardless of the type and number of points, RBF-Galerkin method can use any arbitrary global RBF as trial functions for parameterization and any arbitrary set of points for discretization of the optimal control problem. This property makes our proposed method very flexible in terms of

both interpolant function and discretization points, compared to most of the other numerical methods for solving optimal control problems.

B. Control Approach

A receding horizon control (RHC) approach is developed for the anemia management problem based on the RBF-Galerkin solution proposed. RHC, sometimes called MPC, is an advanced control method that has been in use in various applications, including chemical and oil industries, since the 1980s [31]. It is an efficient approach to design an optimization-based controller for constrained multivariable control problems. The RHC approach to anemia management is as follows: the optimal EPO dose sequence $\left(u^*_{n+1}\ u^*_{n+2}\cdots u^*_{n+N}\right)$, where n is the current time instance, is computed by the RBF-Galerkin method from the current state to the desired state over a finite time horizon t_f. However, only the first dose of the EPO sequence produced (i.e. u^*_{n+1}) is given to the patient, and the state is updated by measuring the patient's current Hb level (Hb_m). The finite horizon optimization problem will be repeated using the updated state $\boldsymbol{x}_{n+1}$, and the recent control u^*_{n+1}, as the initial values for the optimal control problem. The resulting control approach is called the RBF-Galerkin-based RHC method illustrated in Fig. 1.

Multiple Receding Horizon Control (MRHC) Approach: If the patient model is known, the RHC controller shown in Fig. 1 can properly update the EPO dose adjustments by measuring patient's Hb level regularly. However, the individual-based model developed in (1) is indeed dependent on parameters k and τ, which are unknown for new patients, and therefore an MRHC approach is proposed to find the weekly dose of the EPO for each individual patient. Considering the responsiveness of each patient to the anemia drug, there would exist three types of patient groups: poor, average, and good responders. MRHC uses three RHC controllers, one for each patient group, to provide a weighted linear combination of each controller output as the recommended EPO dose for each individual patient. The weight of each controller, ω^l, is inversely proportional to the absolute difference between the previous calculated dose of EPO, u^*_n, and the steady-state value of the EPO for each patient group, u^l_{ess},

$$\omega^l = \frac{1}{1+\left|u^l_{ess}-u^*_n\right|}, \quad for\ \ l=1,2,3. \qquad (19)$$

Also, the control law, u^*_{n+1} (weekly dose of EPO), is calculated as the weighted mean of each controller output,

$$u^*_{n+1} = \frac{\sum_{l=1}^{3}\omega^l u^l_{n+1}}{\sum_{l=1}^{3}\omega^l} \qquad (20)$$

Where $u_{n+1}^{l}, l = 1, 2, 3$, is the current output of each RHC controller. The MRHC control approach for individualized anemia management is illustrated in Fig. 2. According to Fig. 2, each controller represents a different aspect of the dose-response profile, in which RHC 1, RHC 2, and RHC 3 are controllers designed for poor, average, and good responder patients, respectively. In contrast to switching strategy that chooses a single controller output [32], the control action in our proposed approach uses a weighted mean of controller outputs (blending of outputs).

IV. Results

In this Section, the MRHC approach based on the RBFGalerkin optimization method is applied for individualized drug dosing in the anemia management problem. The simulation results of our proposed method are compared with those obtained from a population-oriented approach (AMP) [1] as well as an individual-based method (Smart Anemia Manager or SAM) [18]. The AMP used for this comparison is a clinical protocol for anemia management that has been in use at the University of Louisville Kidney Disease Program (dialysis facility) from 2011 to 2012. SAM, on the other hand, is an individualized method developed by Gaweda et al. [18] and is currently used at the University of Louisville dialysis clinic.

A. Hb measurement without Observational Error

The simulation time is set to 15 months (65 weeks) from starting the treatment and the sampling rate fixed at 7 days. Hb_0 (baseline) is considered to be 8 g/dL, and Hb_T (desired or target) set to 11 g/dL (the midpoint for the Hb recommended range 10–12 g/dL). In addition, it is assumed that the Hb_m (measured) is error free, so there would be no noise in the output. In dialysis facilities, Hb is usually measured weekly, but EPO doses only be adjusted once in a month or every four weeks. To make the simulation results similar to the real case scenarios, we have used the same regulations here (i.e. dose adjustment of every four weeks and weekly measurement of Hb). Achieved Hb levels and EPO dose adjustments computed from MRHC, SAM, and AMP are shown in Fig. 3 and Fig. 4, respectively. Also, three different patient responders including good ($k = 0.94$), average ($k = 0.5$), and poor ($k = 0.3$) responders are considered for the comparison.

B. Hb measurement with Observational Error

Similar to Part A, $t_f = 65$ weeks, $Hb_0 = 8$ g/dL, $Hb_T = 11$ g/dL, and sampling rate of 7 days are considered for the simulation. Also, it is assumed that the Hb concentration is measured weekly and the EPO dose adjusted every four weeks. However, Hb_m is now assumed to be contaminated with the measurement error. A white noise with the maximum amplitude of 0.5 g/dL is added to the output (-0.5 g/dL ≤ Hb error ≤ $+0.5$ g/dL), which is a realistic assumption for the Hb error measured weekly as part of a routine blood test, according to [1]. Achieved Hb level and EPO dose recommendations obtained from MRHC, SAM, and AMP in the presence of Hb measurement errors for good, average, and poor responders are illustrated in Fig. 5 and Fig. 6, respectively.

V. Discussion

FDA recommends individualized anemia treatment with precise control of hemoglobin concentration and minimal drug utilization [9]. In accordance with those recommendations, this work presents an individualized drug dosing approach, called MRHC, by leveraging the theory of optimal control. Performance of the MRHC is compared in silico against a population-based anemia management protocol (AMP) [1] and an individual-based multiple model predictive control method for anemia management [18] in two case scenarios: hemoglobin measurement with and without observational errors. In silico comparison indicates that hemoglobin concentration with MRHC method has less variation among the methods, especially in presence of measurement errors. Also, drug dosages recommended by the MRHC are more stable and accurate and reach the steady-state value notably faster than those generated by the other two methods. Details of the comparison are discussed in this Section.

A. Hb Measurement without Error

According to Fig. 3, while the Hb achieved by the AMP exhibits significant overshoot, both MRHC control method and SAM approach can successfully attain the Hb target of 11 g/dL. There is a considerable difference between MRHC and SAM in terms of the time required to achieve Hb_T. While for good, average, and, poor responders, it took around 44, 51, and 56 weeks, respectively, to hit the Hb target with SAM, this time decreases to 30, 33, and 40 weeks, respectively using the MRHC. In addition, the Hb levels obtained from SAM exhibit small variations for all patient groups, whereas those obtained from MRHC are more monotone and uniformly increasing to the desired level. For all three patient groups (good, average, and poor responders), the performance of AMP is clearly inferior to individual-based methods. Hb levels achieved by the AMP show undesirable wide fluctuations around Hb_T, especially for the initial weeks of treatment. The AMP is also unable to achieve the desired Hb level (11 g/dL) precisely, compared to MRHC and SAM hitting the Hb target.

Fig. 4 illustrates EPO dose adjustments recommended by MRHC, SAM, and AMP. According to Fig. 4, initial doses recommended by the AMP are excessive compared to the optimal steady-state values. This finding is consistent with observations made in real clinical practice. The unnecessarily high initial doses are not only associated with the increased risk of adverse cardiovascular events but also increase the overall cost of treatment. In contrast, both MRHC and SAM are less aggressive with dose recommendations throughout the whole treatment period, starting low and gradually titrating up to the steady-state dose for all three patient groups. For good and average responders, while EPO dose recommendations computed by SAM exhibit undesirable fluctuations around the steady-state level, those produced by MRHC tend to be more consistent. For all three patient groups, doses recommended by MRHC achieve the steady-state level much faster than those generated by the other two methods. In addition, EPO doses produced by MRHC are more stable and uniform than those produced by either SAM or AMP, which is more desirable for the EPO therapy, starting from the lower doses and uniformly increasing to the steady-state level.

B. Hb Measurement with Error

According to Fig. 5-a, all three methods have quite acceptable Hb concentrations achieved for a good responder patient, among which MRHC provides the fastest response with the least fluctuations, and AMP produces the lowest response with the most oscillations. For an average responder, MRHC is significantly faster than the other two methods for attaining the Hb level fairly close to the target. Also, the Hb steady-state level achieved by the MRHC is more accurate than that of the either two methods for an average responder (see Fig 5-b). AMP and SAM seem to have similar performances for achieving the Hb target for an average responder, with the exception that AMP has unnecessary fluctuations for the initial weeks of treatment. For poor responders, MRHC still acts better than the other two methods for rejecting the noise and achieving the desired level within a reasonable time, according to Fig. 5-c. While the Hb concentration obtained from SAM cannot reach the steady-state level within the simulation time (15 months), AMP would be able to keep the Hb in range after around 25 weeks, for a poor responder (Fig. 5-c). However, considering those unnecessary high Hb concentrations for the initial weeks, performance of the AMP is still less efficient than MRHC for the poor responder patients.

Fig. 6 demonstrates EPO dose adjustments recommended by MRHC, SAM, and AMP for different responders with the maximum Hb error of ±0.5 g/dL per measurement. As expected, initial doses recommended by AMP are unnecessarily high for all patient groups. For good responders (Fig. 6-a), AMP acts slightly better than SAM in rejecting the noise and finding the appropriate weekly dose, but for average (Fig. 6-b) and poor responders (Fig. 6-c), doses computed by both methods have undesirable fluctuations and need a relatively long time to achieve the steady-state level. On the other hand, EPO dose adjustments by the MRHC tend to be more stable and accurate in presence of measurement errors and also reach the steady-state value notably faster than those generated by the other two methods. More interestingly, comparing EPO doses recommended by MRHC for two cases, Hb measurement without error (Fig. 4) and with error (Fig. 6), reveals that weekly doses are exactly the same for similar patient groups. In contrast, EPO doses found by AMP and SAM are adversely affected by the measurement error. This indicates that the MRHC approach is more immune to noise than the other two methods and can be successfully applied as a robust approach for the anemia management problem.

VI. Statistical Comparison

In this section, 40 hypothetical CKD patients with different responsiveness to medication, k, and red cell turnover, τ, are considered for the simulation. Also, three different methods, including MRHC, SAM, and AMP, are applied to control the Hb concentration in patients. It is assumed that all patients have the baseline Hb of 9 g/dL and the goal is to attain the target Hb of 11.5 g/dL. The simulation is divided into two parts. The first 12 months are called the transient cycle (even though it usually takes less time for all methods to attain the Hb target, transient cycle is assumed 12 months to ensure the Hb steady-state level has been achieved), followed by the steady-state period for the next 6 months. A random error of ±5% is added to the simulation to account for the measurement errors as well as factors that have not been included in the model such as infections or hospitalizations. Please note that baseline Hb,

target Hb, and simulation time are deliberately assumed different than those values used in Section IV to make a new scenario for the statistical comparison between the methods.

Table I compares the mean values for average achieved Hb level (per patient), standard deviation of achieved Hb level (per patient), and absolute difference between the average achieved Hb level and Hb target (11.5 g/dL) obtained from MRHC, SAM, and AMP for the steady-state period of treatment. Among mean values of the average achieved Hb level, MRHC achieves the closest value to the target, while AMP results in the lowest mean, which is still in the range but far from the target. Comparison of mean values for the standard deviation of the Hb level reveals that MRHC and AMP have less variation of the achieved Hb level than SAM, which is expected considering the fluctuating output of SAM in presence of measurement error, especially for poor responders (see also Fig 5-c). Comparing the absolute difference between the achieved Hb level and Hb target, which is a measure of accuracy for methods, shows that our proposed method achieves the lowest value of 0.12 ± 0.03 g/dL, and hence is very successful in achieving the desired Hb level compared to SAM and AMP. It simply means that by choosing the RBF-Galerkin-based MRHC approach among these three methods:

1. The average Hb level achieved for each simulated patient is relatively close to 11.5 g/dL (efficacy of proposed method).
2. Standard deviation of the achieved Hb level for each simulated patient would be relatively close to zero, i.e. the lowest standard variation among three methods, (reliability of proposed method).

By applying the F-test from analysis of variance (ANOVA), we test the hypothesis about the equality of mean values of average achieved Hb level from MRHC, SAM, and AMP. The ANOVA results in F-Value=112.94 and P-value=0.000, meaning that mean values are significantly different. Post-ANOVA pairwise comparison of means using the Tukey test with 99% confidence interval (CI) is demonstrated in Fig. 7. Please note that if an interval does not contain zero, the corresponding means are significantly different. Fig. 7 clearly indicates that mean value of average achieved Hb level from each method is significantly different than that of the other two methods.

We also test the hypothesis if the mean values of absolute difference between the average achieved Hb level and Hb target for MRHC, SAM, and AMP are equal. ANOVA results reveal that mean values are notably different (F-Value=110.98 and P-value=0.000). Also, Tukey method with 95% CIs indicates that there are considerable differences between the mean values of MRHC and AMP, also between the means of MRHC and SAM as well as means of SAM and AMP, for the absolute difference between the achieved Hb level and Hb target (see Fig. 8).

VII. Conclusion

An MRHC control approach based on the RBF-Galerkin optimization method has been proposed for individualized drug dosing in the anemia management problem. Anemia management has been formulated as a constrained optimal control problem solved by the RBF-Galerkin method numerically. Then a multiple receding horizon controller was built

based upon the optimization algorithm to precisely control and achieve the desired Hb concentration for individual patients. Simulation results have been compared with those obtained from a population-oriented approach (AMP) as well as an individual-based method (SAM) for anemia management to evaluate the efficiency of the proposed method. In silico comparison between our proposed method and two other approaches has indicated that Hb concentration with MRHC had less variation among the methods, especially in presence of measurement errors. In addition, EPO dosages computed by our proposed method were more stable and more accurate, also reached the steady-state value notably faster than those generated by the other two methods. Results of statistical comparison demonstrated that the mean of the average achieved Hb level from the MRHC has been significantly closer to the Hb target than that of the other two methods. Also, the results of Tukey test demonstrated that the absolute difference between the achieved and target Hb for our proposed method was notably lower than those for the other two approaches, confirming the efficacy of the proposed method for the anemia management problem.

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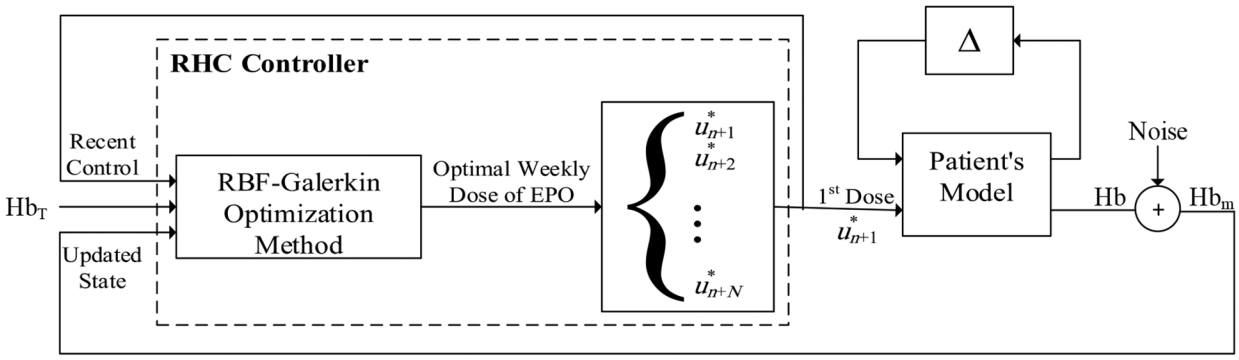

Fig. 1.

Block diagram of RHC controller based on the RBF-Galerk in method for anemia management

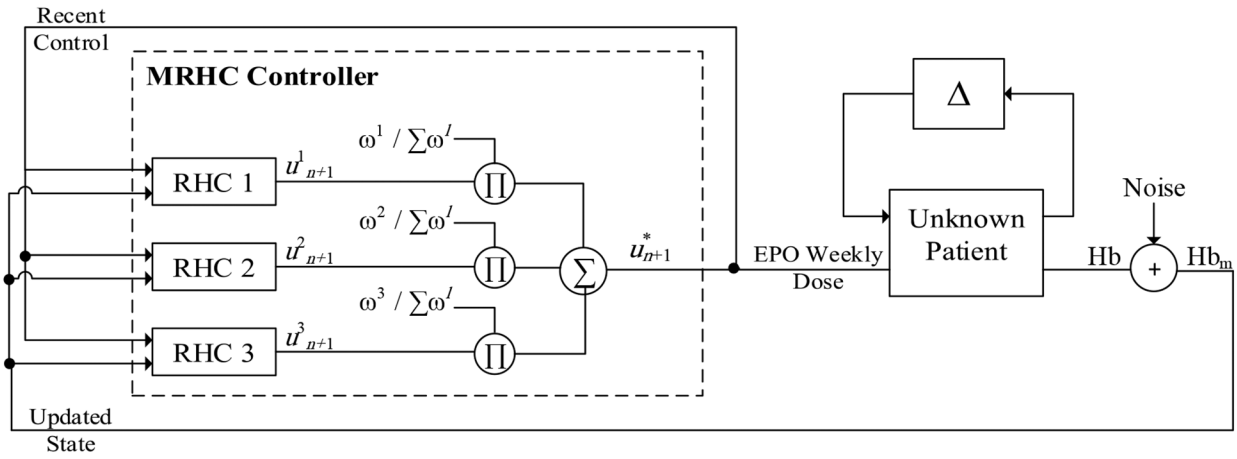

Fig. 2.
Multiple receding horizon control (MRHC) approach for individualized anemia management

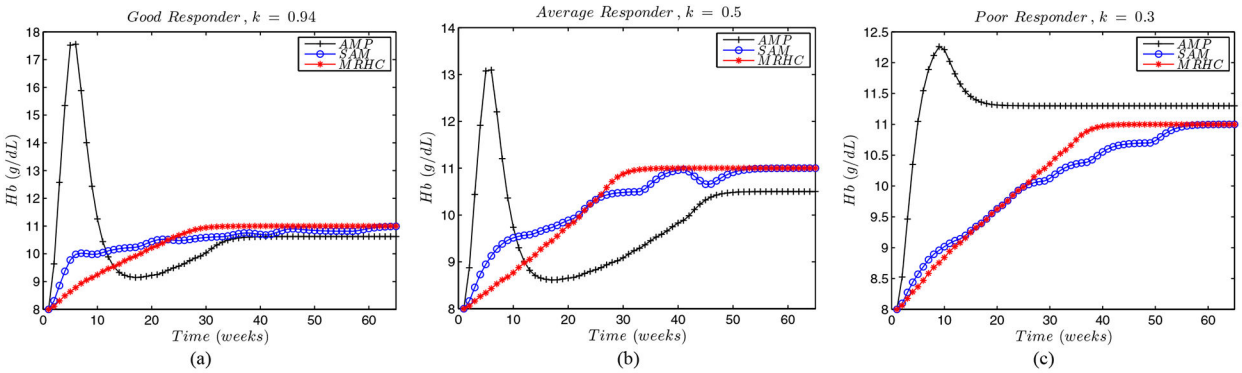

Fig. 3.

Achieved Hb level obtained from MRHC (proposed method), SAM, and AMP for a) good, b) average, and c) poor responder patients

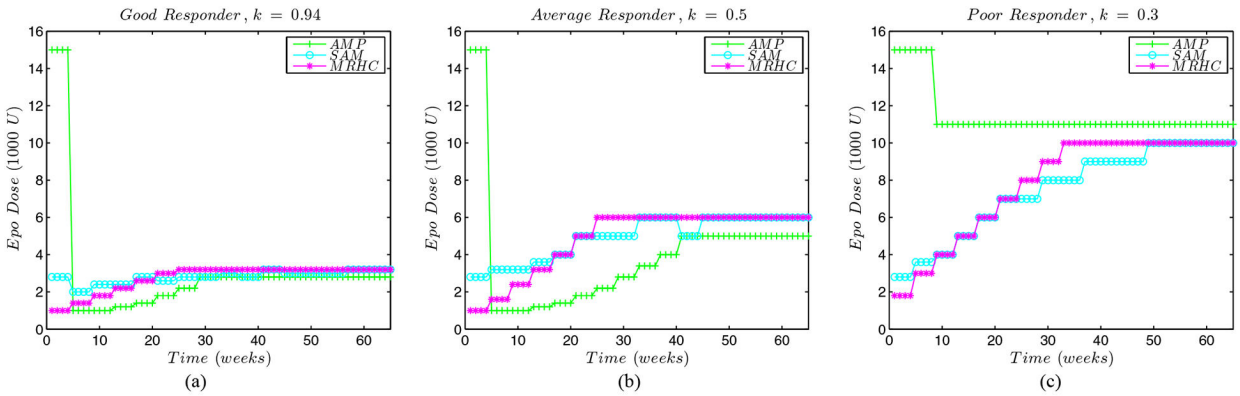

Fig. 4.

EPO dose adjustments computed by MRHC, SAM, and AMP for a) good, b) average, and c) poor responder patients

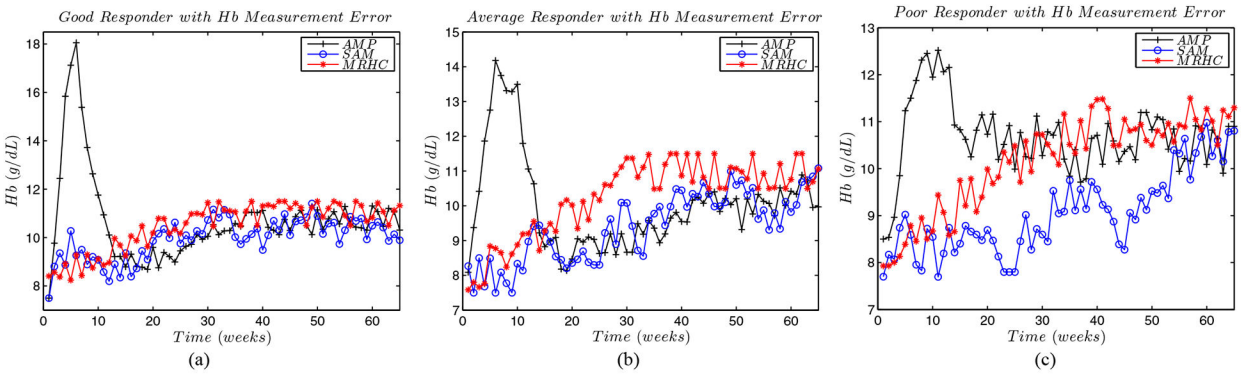

Fig. 5.

Achieved Hb level with Hb measurement error obtained from MRHC, SAM, and AMP for a) good, b) average, and c) poor responder patients

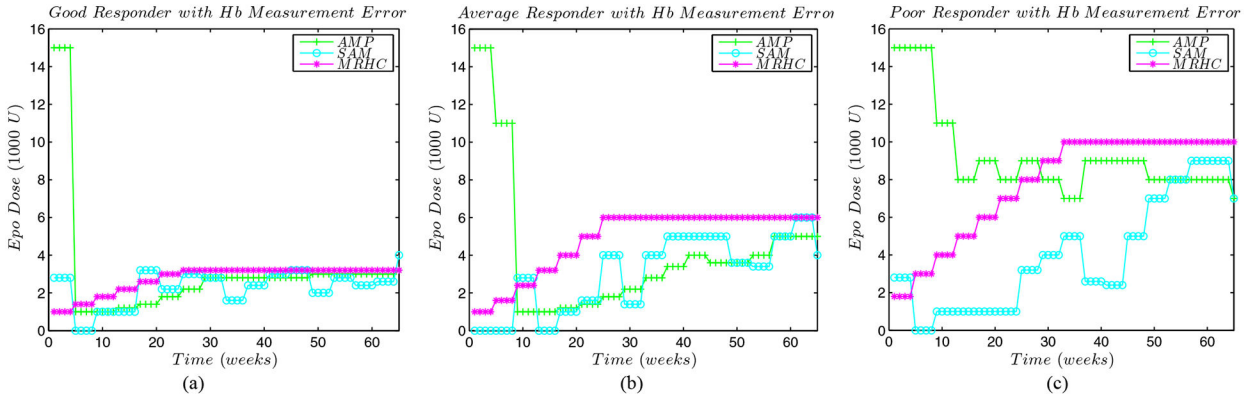

Fig. 6.

EPO dose adjustments in presence of Hb error computed by MRHC, SAM, and AMP for a) good, b) average, and c) poor responder patients

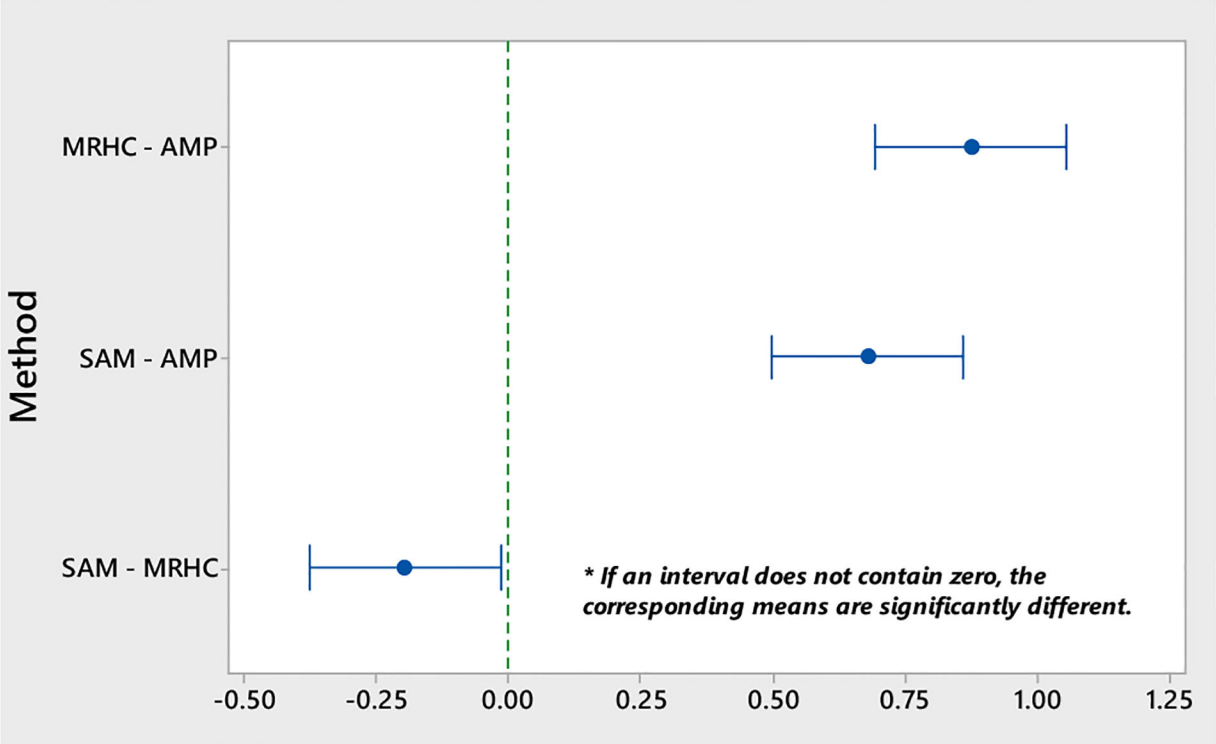

Fig. 7.
Differences of means for the average achieved Hb level (Tukey Test with 99% CIs)

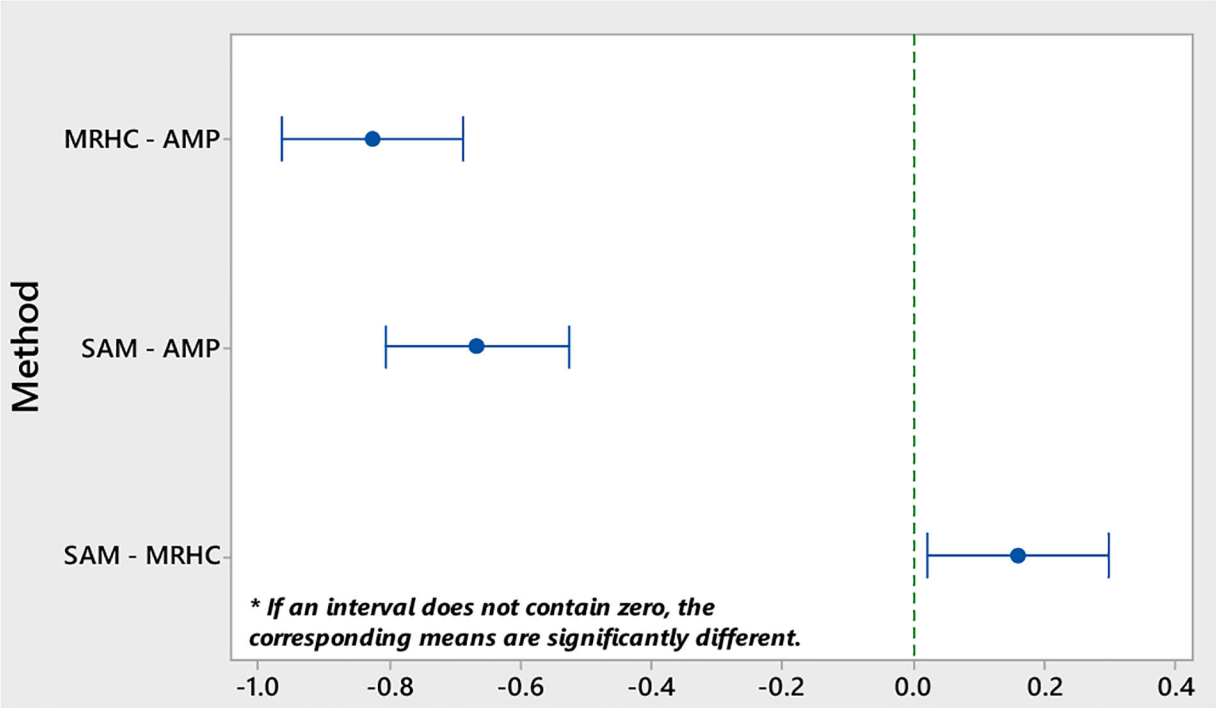

Fig. 8.

Differences of means for the absolute difference between the achieved Hb level and Hb target level (Tukey Test with 95% CIs)

TABLE I

Statistical Comparison of Mean Values of MRHC, SAM, and AMP for Anemia Management

	MRHC	SAM	AMP
Average Achieved Hb Level (g/dL)	11.432±0.043	11.237±0.094	10.558±0.104
SD for Achieved Hb Level (g/dL)	0.358±0.010	0.468±0.021	0.391±0.015
Absolute diff. Achieved Hb & Target Hb (g/dL)	0.117±0.031	0.276±0.090	0.942±0.104