Precise Warfarin Management through Personalized Modeling and Control with Limited Clinical Data

Syed Irfan Ali Meerza, Affan Affan, Hossein Mirinejad, Michael E. Brier, Jacek M. Zurada and Tamer Inanc

Abstract— Warfarin belongs to a medication class called anticoagulants or blood thinners. It is used for the treatment to prevent blood clots from forming or growing larger. Patients with venous thrombosis, pulmonary embolism, or who have suffered a heart attack, have an irregular heartbeat, or prosthetic heart valves are prescribed with warfarin. It is challenging to find optimal doses due to inter-patient and intra-patient variabilities and narrow therapeutic index. This work presents an individualized warfarin dosing method by utilizing the individual patient model generated using limited clinical data of the patients with chronic conditions under warfarin anticoagulation treatment. Then, the individual precise warfarin dosing is formalized as an optimal control problem, which is solved using the DORBF control approach. The efficiency of the proposed approach is compared with results obtained from practiced clinical protocol.

Clinical Relevance– This establishes a framework for achieving personalized precise warfarin dosing strategies by utilizing personalized models and modern control techniques from limited clinical data.

I. INTRODUCTION

Warfarin is a commonly prescribed oral anticoagulant to prevent fatal blood clots in patients. In older adults, warfarin is drug-related source of adverse effects [1]. A blood test called international normalized ratio (INR) of prothrombin duration is used to track the effects of warfarin. The therapeutic INR range is narrow: 2.0–3.0 in most cases [2] and 2.0–2.5 in patients with coronary heart disease who need antiplatelet and anticoagulation therapy [3]. When the warfarin dose is too high, internal bleeding occurs, and when the dosage is low, stroke occurs. Narrow therapeutic range, along with a ten-fold disparity makes clinical control of warfarin much more complex [4].

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The warfarin dose calculation equations suggested by Gage [5] and the International Warfarin Pharmacogenetics Consortium (IWPC) [4] are most widely used in clinical practice today. Gage used least square regression to predict dosage in their work, where they used median absolute error to measure accuracy. Although their model takes the patient's race into account, their data consists of primarily European patients. IWPC used a similar approach as Gage, but they had significantly large and diverse data [4]. In their work Yu [6] have used multivariate regression equation to study VKORC1 (-1639G>A) and CYP2C9 genotype cases with heart valve replacement. As the warfarin clinical data grew larger, machine learning methods [7], Bayesian decision [8], boosted regression tree [9], artificial neural networks (ANNs) [10], and reinforcement learning [11] have been used by researcher to find precise warfarin dosage. However, an individualized dosing approach should have the benefit of being encumbering a specific patient without relying on general population data.

The administration of warfarin can be modeled as a constrained optimal control problem, in which the desired INR level is set between 1.5-2. Medical restrictions, such as the maximum daily dose, the rate of change in INR, and the rate of change in dosage, may impose these constraints. For the individualized warfarin dosing problem, we implemented the Radial Basis Function-Galerkin method developed by Mirinejad et al. [12] [13] as a general optimal control problem-solving framework and developed a Receding Horizon Control (RHC) approach to provide a precise warfarin dose. The individualized models we have used are derived from limited clinical patient-specific data using semi-blind system identification techniques [14]. Results have been compared with the results of clinical practice warfarin management guidelines [15].

The paper is organized as follows: Section 2 presents the individualized patient models and the warfarin management problem as an optimal control problem. Section 3 presents the results and comparison of the proposed RHC and WMP. Finally, the conclusions are given in Section 4.

II. WARFARIN MANAGEMENT PROBLEM

A. Individualized Patient Model from limited clinical patient-specific data

Patient-specific warfarin dosing data were obtained from a study of warfarin pharmacodynamics in 162 subjects performed at the Robley Rex Veterans Medical Center, Louisville, KY. Patient data were obtained by retrospective review and through an informed consent process. To find the

model for each patient, we have used a Semi-blind robust identification technique that considers the initial conditions of the patient [14]. The problem statement for Semi-blind identification can be briefly defined as follows:

Problem 1: 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 non-empty set.

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

where $g_0 = D_g; g_i = C_g(A_g)^{i-1}B_g$. Problem (1) is a non-convex, NP-hard problem which can be converted into the convex problem, given in [16], as follows:

Problem 2: Determine $G(z)$ such that τ is non-empty set:

$$\tau(y) = \left\{ G(z) \in S : y_i - (T_g^N u)_i + (\Gamma_g^N u^-)_i \right\} \quad (2)$$

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 plant response for input u, and the later part provides information for plant response for past inputs u^-. This problem can be solved by LMIs as presented in [16]. The individualized models of patients number 33 and 40 obtained by the semi-blind identification technique are given in Eqs. 3, and 4, respectively.

$$G_{33}(z) = \frac{0.0591z^3 - 0.0469z^2 + 0.0014z - 0.78^{-3}}{z^3 - 1.612z^2 + 0.7558z - 0.134} \quad (3)$$

$$G_{40}(z) = \frac{0.246z^3 - 0.22z^2 + 0.085z - 0.0074}{z^3 - 1.69z^2 + 0.8817z - 0.1823} \quad (4)$$

B. Warfarin Management Protocol

Warfarin management protocols (WMP) are guidelines for the warfarin dose to be provided. These guidelines are the range of possible dosages availabe in tables for different INR levels in different categories of patients. These guidelines make recommendations based on the facts presented in the American College of Chest Physicians Clinical Practice Guidelines (CHEST) report [17]. WMP guidelines provide a range of standardized dosage of warfarin for a population of patients as a whole and do not provide any precise individualized dosage.

C. Precise Warfarin Management Problem Statement

The dosage of warfarin is determined by a number of factors, including the current INR level, the rate at which the INR level changes, the maximum dose of warfarin, and so on. The warfarin dosage problem can be viewed as an optimal control problem by formalizing the individualized drug-dose response model for each patient. As we have used first 5 days dose-response data to find the patient model, the INR at 5th day is considered as the baseline INR (INR_0). The healthy INR level is considered to be in range of 1.5-2,it is called target INR (INR_T). The one time maximum warfarin dose allowed is 20mg, and the warfarin dose variation per week should be in the range of ±50%. Warfarin dosing can be formulated as an optimal control problem as below.

$$Minimize \quad J = \int_{t_0}^{t_f} ((x_2(t) - \alpha)^2 + (u(t) - \alpha)^2)dt \quad (5)$$

subject to system equations,
$$\dot{x_1}(t) = ax_1(t) + bx_2(t) + ... + cu(t)$$
$$\dot{x_2}(t) = x_1(t) \quad\quad\quad\quad\quad\quad\quad\quad (6)$$
$$y_1(t) = x_2(t) + I_0 \quad , \quad y_2(t) = x_1(t)$$

box constraints, and initial conditions,

$$0 \leq u(t) \leq 20 \, , \, -0.5u(t-1) \leq | \dot{u}(t) | \leq 0.5u(t-1)$$
$$x_1(0) = 0 \, , \, x_2(0) = 0 \, , \, u(0) = 0 \quad\quad (7)$$

where system equations coresponds to the individualized models, a, b, c are constants, $u(t), \dot{u}(t), y_1(t)$, and $y_2(t)$ are warfarin dose, warfarin dose derivative, INR level, and rate of change of INR, respectively.

D. Radial Basis Function (RBF)-Galerkin Solution

RBF-Galerkin is a numerical solution methodology that solves Eq. (6)–(7) optimal control problem, by interpolating global RBFs on an arbitrary set of collocation points [18]. To solve the warfarin dosing problem, $x(t) = [x_1(t) \, x_2(t)....]^T$ and $u(t)$ are approximated using N global RBFs within $[0 , t_f]$ as

$$x(t) = x^R(t) = \sum_{i=1}^{N} \alpha_i \varphi(|| t - t_i ||) = \sum_{i=1}^{N} \alpha_i \varphi_i(t)$$
$$u(t) = u^R(t) = \sum_{i=1}^{N} \beta_i \varphi(|| t - t_i ||) = \sum_{i=1}^{N} \beta_i \varphi_i(t) \quad (8)$$

where $x^R(t)$ and $u^R(t)$ denotes the RBF approximation of $x(t)$ and $u(t)$, respectively. $\varphi_i(t)$ is the radial basis function and α_i, β_i are RBF weights related to $x^R(t)$ and $u^R(t)$, respectively. The optimal control problem is then discretized using equally-spaced nodes τ_j , j =1,2,...,N, distributed over the interval $[0, t_f]$ given by $\tau_1 = 0$, $\tau_N = t_f$. The integral cost function of (5) is also approximated by the Chebyshev-Gauss quadrature as

$$J = \frac{t_f}{2} \sum_{j=1}^{N} w_j((x_2^R(t) - \alpha)^2 + (u^R(t) - \alpha)^2) \quad (9)$$

where w_j are weights corresponding to equally-spaced nodes, on the other hand, the differential equations of (6) are transcribed into algebraic equations using Gaussian differentiation matrix [19] to transcribe the optimal control problem of (5)–(7) into a Non-Linear Programming (NLP) problem where the decision variables are RBF weights [20]. The NLP problem can be straightforwardly solved using NLP solvers such as SNOPT [21].
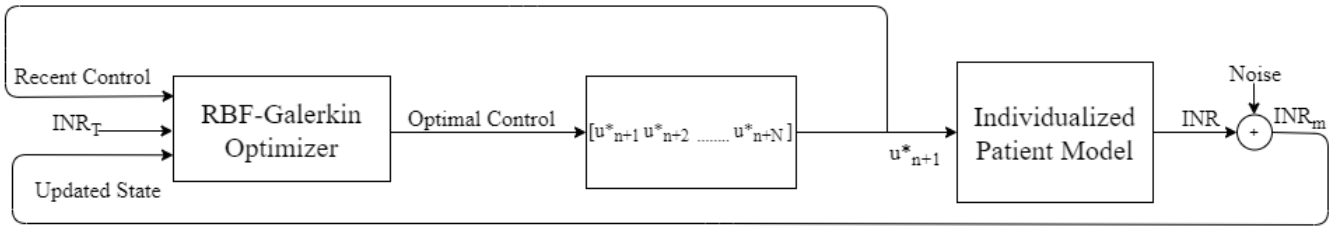
Fig. 1. Receding horizon controller based on the RBF-Galerkin method for individualized precise warfarin dosing

E. Receding Horizon Control (RHC) Approach

In RHC constrained optimization problems are solved over a time horizon by repetition where the cost of the problem, disturbances and the constraints are used in each iteration [22]. The constraints are used as the limits on the control variables and feed forward actions are generated. RHC is easier to compute than steady state optimal control, it is adaptive to parametric changes than infinite horizon control, it tracks better than PID, and it features better constraints handling among the others [23]. The optimal warfarin dose sequence (u^*_{n+1} u^*_{n+2} ... u^*_{n+N}), 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 from the computed warfarin sequence (i.e., u^*_{n+1}) is given to the patient, and new states x_{n+1} are computed for the patient by measuring the current INR level (INR_m). The exact process will be repeated using the updated state and the recent control u^*_{n+1} as the initial values for the next iteration. The resulting control approach is illustrated in Fig. 1.

III. RESULTS AND DISCUSSION

In this work, we have used first 5 days clinical data of each patient to create individual patient models and find out the optimal dosage of warfarin and respective INR level using RBF-Galerkin controller and WMP. So the treatment starts from sixth day with current INR as baseline INR and 1.5 as target INR. The treatment time frame is 52 days. INR level and warfarin dosage produced by the RBF-Galerkin-based RHC are then compared with those obtained from the clinical WMP to examine the efficiency of our method. The warfarin dosage generated by the WMP or the RHC is a daily dosage, but the changes are made weekly.The warfarin dose comes in different tablet strengths: 1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg [24]. Therefore, we have quantized the daily dosage so that the required daily dose can be taken by one tablet. In both cases, zero warfarin dose is allowed, which means no warfarin dose for a day or two; if the patient's INR level is higher than 4.1 [15]. Furthermore, to make the simulations more realistic, we have added measurement error (due to error in apparatus or human reading error) in the INR level as a form of random noise. The results for both with and without measurement error cases are discussed as follows. Achieved INR levels and warfarin dose adjustments computed from RBF-Galerkin RHC and WMP for patients #33 and 40 in the patient dataset are shown in Fig. 2-3. In the figures

the red vertical line is the identification point from where the treatment using RHC or WMP starts, before that point are the clinical data. It can be seen from the figures that RHC reaches the target INR level faster while WMP tries to keep the INR level in the healthy range of 1.5-2. The RHC provides us a stable warfarin dosage to keep the INR level near the target value. The measurement noise we have added to the INR output is a white noise with the maximum amplitude of 0.3 (-0.3 ≤ INR error ≤ +0.3). Fig. 4-5 shows the achieved INR levels and warfarin dose adjustments with measurement error for patients #33 and 40. It is clear from the figures that the measurement noise has a negligible effect on the RHC outputs, while in the case of WMP, the results are significantly affected. From the results, we can see that WMP overshoots the INR level, while RHC tries to use the minimum possible warfarin dose, which can increase the patient's INR level near the target value. Another advantage of RHC over the WMP is that we can select a target INR level in RHC, making the patient's INR more stable with an optimal warfarin dosage. However, the WMP tries to keep the INR level within a range, making the INR fluctuate in the patient's body with a regularly changing warfarin dose.
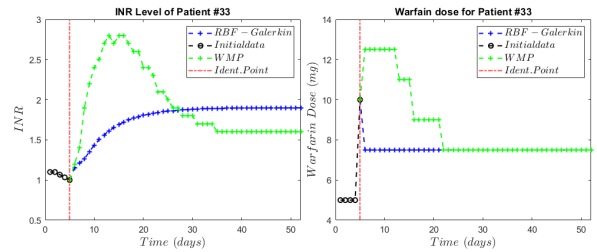

Fig. 2. INR level and warfarin dose adjustments obtained from RHC (proposed method), and WMP for patient-33
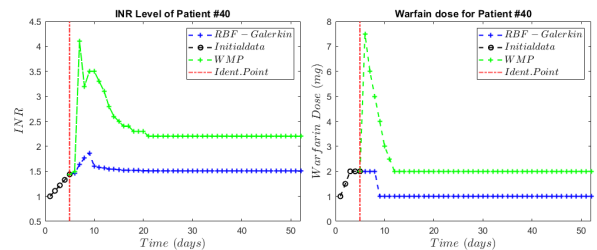

Fig. 3. INR level and warfarin dose adjustments obtained from RHC (proposed method), and WMP for patient-40

IV. CONCLUSION

An individualized precise warfarin management algorithm has been developed based on the RBF-Galerkin optimization method with the individualized patient model derived from limited patient-specific clinical data. We formulated the warfarin management problem as a constrained optimal control problem and numerically solved it using the RBF-Galerkin method. RHC approach was used with the optimization algorithm to precisely control the INR level and warfarin dose. Results were compared with those obtained from WMP to evaluate the efficiency of the proposed method which indicated that RHC tried to keep INR stable throughout the time frame, even under measurement errors while tracking the target INR level. Furthermore, warfarin dosages computed by our approach were more stable, accurate and reached the steady-state value notably faster.

V. ACKNOWLEDGMENT

Fig. 5. INR level and warfarin dose adjustments obtained from RHC (proposed method), and WMP for patient-40 in presence of INR measurement error

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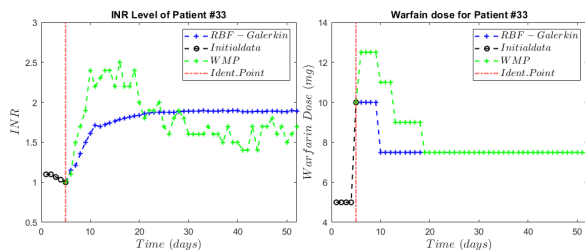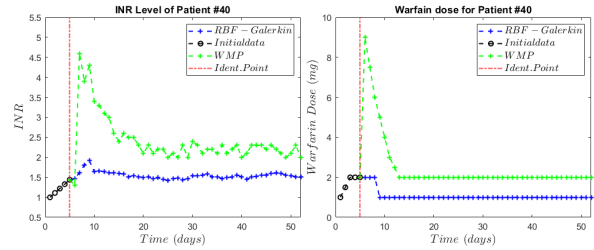
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Fig. 4. INR level and warfarin dose adjustments obtained from RHC (proposed method), and WMP for patient-33 in presence of INR measurement error