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Clinically Relevant Adaptive Modeling for Personalized Drug Dosing

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***Abstract*—Drug delivery for warfarin and anemia management is a difficult task due to narrow therapeutic range and change in patient's Pharmacokinetic (PK) and Pharmacodynamic (PD) due to change in patient's life habits. To assist the clinicians, this paper present a clinical decision support system based on the semi-blind robust system identification with model (In)validation framework to develop adaptive individualized patient models. These models can be utilized in feedback control design algorithms to suggest optimal drug dosage. The preliminary results show that the adaptive individualized patient models accurately predicts individual patient's true dose-response characteristics by adapting to the changes in the patient's current health status.**

***Index Terms*—Anemia management, adaptive modeling, drug dosing, individualized patient modelling, model (In)validation, robust system identification, warfarin management.**

I. Introduction

Administration of drugs has been a challenging task for anemia and warfarin management due to narrow therapeutic range, altered pharmacokinetics with disease progression, and dosing restrictions. In anemia management, the external human recombinant erythropoietin (EPO) is used weekly to keep the hemoglobin (Hb) levels between 10-12 g/dl of chronic kidney disease (CKD) patients [1], [2]. In warfarin management, the warfarin is used to keep the International Normalized Ratio (INR) between 2.0 and 3.0 to avoid thromboembolic events [3], [4]. The drug dosing becomes more challenging when patients' dose-response status changes due to aging, change in food propensities, and another drug usage for another illness. Numerous dosing protocols have been proposed based on average, population-based responses to medications [5]– [7]. These methods are failed to address the large inter and intra-variability among patients, leading to unintentional improper dosing resulting in severe health risks. Therefore, individualized and precise drug dosing methods are required. This research aims to develop a clinical decision support system to determine optimal drug dosage using adaptive individualized patient modeling from limited, patient-specific clinical data and feedback control theory [8]– [14]. The proposed system is evaluated *in slico* to the cases of precise anemia management and warfarin management.

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II. Methods

In this research, we have developed adaptive individualized patient modelling framework using semi-blind robust system identification technique and model (In)validation technique to identify and update the patient model whenever model is no longer suitable for dosage prediction and controller design.

A. Adaptive Individualized Patient Modelling

Semi-blind robust system identification framework aims to develop patient model, H, using N input (dosage) and output (measurement) data points of the patient response [9]– [11]. Semi-blind robust system identification utilizes non-zero initial conditions to reduce the identification error. The problem statement for semi-blind robust system identification can be written as:

Problem 1: Determine $H = \begin{bmatrix} A_h & B_h \\ C_h & D_h \end{bmatrix}$, which is compatible with patient's clinical data, such that τ is a non-empty set:

$$\tau\left(y\right) = \left\{H\left(z\right) \in S : y_i - \left(T_h^N u^+\right)_i + \left(\Gamma_{\mathrm{h}}^{\mathrm{N}} u^-\right)_i\right\} \qquad (1)$$

where $i = 1, \cdots, N$, u^- is non-zero initial conditions, T_h^N is the Toeplitz matrix and Γ_{h} is Hankel matrix.The details can be found in [8], [9]. To validate the model for practical use, the latest clinical data, not used during identification process, of the same patient is used. The problem statement for model (In)validation can be written as follows [9], [14]:

Problem 2: Given latest clinical data points (y_i, u_i), the model $H\left(z\right)$, and initial conditions x_0, determine if there exists at least one combination of $(\eta,\ \Delta, x_0)$ that can reproduce the available clinical patient data:

$$y = \left(I + \Delta\right)\left(T_h u + \Gamma_{\mathrm{h}} u^- + \ \bar{\eta}\right) \qquad (2)$$

Equation (2) is satisfied if a triple $(u^-, \bar{\eta}, \Delta)$ exists and $\|\Delta\|_\infty < 1$.

III. Results

To demonstrate the proposed framework, the clinical data of fourty-six patients for warfarin management and fifty patients for anemia management cases have been collected from Robley Rex Veterans Administration Medical Center and Kidney disease program, University of Louisville, USA, respectively.

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The prediction results of the identified adaptive individualized model of patient ID # 21 for anemia management are shown in Fig. 1. The model prediction results for the adaptive model

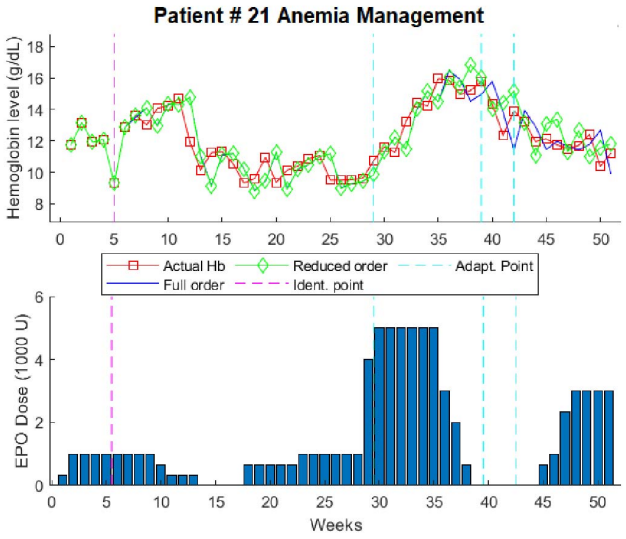

Fig. 1. The prediction results for adaptive individualized model of patient ID # 21 for anemia management.

of patient ID # 147 for warfarin management are given in Fig. 2. The results show that identified patient-specific

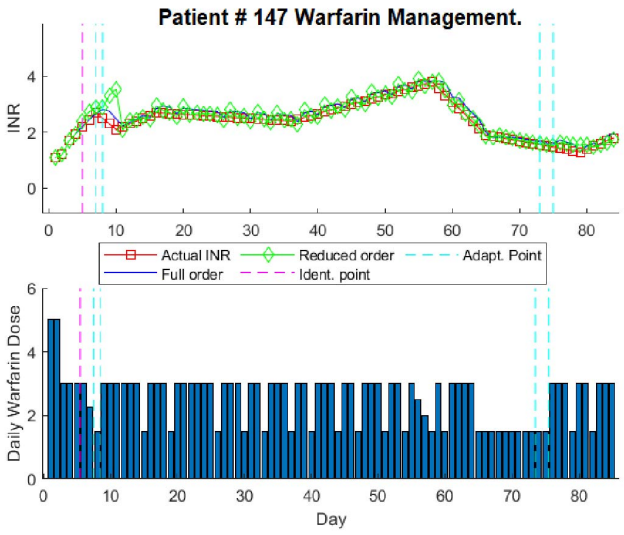

Fig. 2. The prediction results for adaptive individualized model of patient ID # 147 for warfarin management.

models predicted dose-response of patients with high accuracy. The proposed framework is able to adapt the individualized models according to the data fluctuation in time and current patients' status. The minimum mean squared error (MMSE) results show that the prediction errors for warfarin and anemia management are 0.078 ± 0.044 and 1.4 ± 0.5, respectively.

IV. Conclusion

In this research, semi-blind robust system identification technique with model (In)validation is used to develop clinical decision support system. The proposed system provides adaptive individualized patient models from a limited number of patient-specific clinical data for single drug dosing and it is evaluated on the cases of anemia management and warfarin management. The preliminary results showed that the identified models predicted the patients' dose-response characteristics with high accuracy.

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References

[1] Valderrábano, "Erythropoietin in chronic renal failure," Kidney International, vol. 50, no.4, pp. 1373-1391, 1996.

[2] M. Panjeta, I. Tahirovic, J. Karamehic, E. Sofic, O. Ridic and J. Coric, "The Relation of Erythropoietin Towards Hemoglobin and Hematocrit in Varying Degrees of Renal Insufficiency," Materia socio-medica, vol. 27, no. 3, pp. 144-148, 2015.

[3] S. Shikdar, "International Normalized Ratio (INR)," StatPearls [Internet]., 10-May-2021. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK507707

[4] N. A. Limdi, "Warfarin Pharmacogenetics: Challenges and Opportunities for Clinical Translation," Frontiers in Pharmacology, vol. 3, no. 183, 2012.

[5] R. Bellazzi, "Drug Delivery Optimization through Bayesian Networks: An Application to Erythropoietin Therapy in Uremic Anemia," Computers and Biomedical Research, vol. 26, no. 3, pp. 274-293, 1996.

[6] J. D. Martin Guerrero, E. S. Olivas, G. C. Valls, A. J. Serrano López, J. J. Pérez Ruixo and N. V. Jiménez Torres, "Use of neural networks for dosage individualisation of erythropoietin in patients with secondary anemia to chronic renal failure," Computer in Biology and Medicine, vol. 33, no. 4, pp. 361-373, 2003.

[7] A. Sharabiani, A. Bress, E. Douzali, and H. Darabi, "Revisiting Warfarin Dosing Using Machine Learning Techniques," Computational and Mathematical Methods in Medicine, vol. 2015, pp. 1–9, 2015.

[8] A. Affan, J. M. Zurada, and T. Inanc, "Adaptive Individualized Modeling from Limited Clinical Data for Precise Anemia Management," IEEE Access, pp. 1–10, 2021.

[9] M. Wenjing, "Semi-blind Robust Identification and Model (In)Validation," Ph.D. thesis, Pennsylvania State University, Pennsylvania, USA, 2006. [Online]. Available: https://etda.libraries.psu.edu/catalog/8026

[10] T. Inanc, M. Sznaier, P. A. Parrilo and R. S. Sánchez Peña, "Robust identification with mixed parametric/nonparametric models and time/frequency-domain experiments: theory and an application," IEEE Transactions on Control Systems Technology, vol. 9, no.4, pp. 608-617, 2001.

[11] R. S. Sánchez-Peña and M. Sznaier, "Robust Systems Theory and Applications", New York: Wiley, 1998.

[12] H. Mirinejad, A. E. Gaweda, M. E. Brier, J. M. Zurada and T. Inanc, "Individualized drug dosing using RBF-Galerkin method: Case of anemia management in chronic kidney disease," Computer Methods and Programs Biomedicine, vol. 148, pp. 45-53, 2017.

[13] E. Akabua, T. Inanc, A. Gaweda, M. E. Brier, S. Kim and J. M. Zurada, "Individualized model discovery: The case of anemia patients," computer methods and programs in biomedicine, vol. 118, no. 1, pp. 23-33, 2014.

[14] Y. Muhittin, "Robust Systems Theory Applications to Macroeconomic Stabilization Problems," Ph.D. thesis, Pennsylvania State University, Pennsylvania, USA, 2005. [Online]. Available: https://etda.libraries.psu.edu/catalog/6870