A Cascaded Regression Approach For Precision Medication Dosing

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***Abstract*— We present a cascaded generalized linear modeling approach, which generates a personalized medication dosing policy for patients in critical care environments. We validated our approach using retrospective data from 4,470 patients extracted from a publicly available clinical data archive. We have found our approach to be nearly twice as effective (1.87) in classification of patient state (under-dosed, over-dosed, or therapeutic) when compared to the performance of clinicians. This paper is an important illustration of how to leverage large-scale retrospective clinical databases to develop precision clinical policies. Our approach is particularly valuable in the case of medication dosing, where clinical trials are unable to dose highly ill patients, or provides doses at levels that may be deemed "unsafe". Hence, retrospective analysis, like ours, allows us to more precisely characterize this personalized dose-response relationship.**

I. Objective

Deviations from medication dosing protocols in a complex clinical environment such as the intensive care unit (ICU) are common. Some of these deviations are errors, which can result in harmful outcomes while others are innovative adjustments made by clinicians to adapt to the unique characteristics of an individual patient. For many drugs, these errors are harmless; however, misdoing medications with sensitive therapeutic windows, such as heparin, can place patients at unnecessary risk, increase length of hospital stay, and waste hospital resources. In this work, we present an online method, which provides an individualized dosing policy using a cascaded generalized linear modeling approach. The method begins by proposing an initial heparin dose based on population level features, and prescribes subsequent dose estimates based on increasingly available laboratory measures, and other data from the individual patient [1].

II. Methods

We employed retrospective data from 4,470 patients, extracted from the publicly available Multiparameter Intelligent Monitoring In Intensive Care (MIMIC) database [2]. Our extracted features included heparin dose level, comprehensive laboratory measurements, and all known static confounders of heparin dosing according to the literature. Our continuous outcome measure was active partial thromboplastin time, cast as a categorical variable measuring aPTT therapeutic state: therapeutic, subtherapeutic and supratherapeutic.

We utilized logistic regression to model the probability of supra- and sub-therapeutic aPTT as a function of our selected features. The probability of therapeutic aPTT was then inferred from these estimates. For the initial dose, population level data was utilized to estimate model coefficients. At each subsequent dose modification, model parameters were re-estimated by weighting individual data in the SSE cost function. The weighting function for the individuals was inferred using scatter-search. This approach consists of weighting incoming patient data in a cascaded GLM to construct an increasingly personalized model that describes the dose-outcome relationship for the individual.

III. Results

After applying leave one out cross validation (LOOCV), our model was observed to be nearly twice as effective (1.87) in classification of patient state when compared to the clinicians (assuming clinicians aimed to bring subjects to the therapeutic state). Importantly, this improvement in classification tapers off in later dose adjustments when using the initial population-based model alone. The individualized mode, however, exceeds the performance of the clinician at both the initial, and all subsequent heparin dose adjustments (33% in the best case, and 15% in the worst case.).

IV. Discussion

This paper illustrates the utility of large-scale retrospective clinical databases in improving quality of care. Retrospective data is particularly useful in cases like medication dosing, where clinical trials are unable to dose patients at levels that may be deemed "unsafe", and clinician trial participants may not be representative of those undergoing care. Our results demonstrate that a sequential modeling approach learned from retrospective data, could potentially be used at the bedside to improve the ability to understand the relationship between dose, and therapeutic outcome for individualized patients.

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