CS 234, Winter 2023
Stanford University

E

Abstract

Warfarin is the most widely used oral blood anticoagulant agent worldwide, with **over 30 million prescriptions** in the United States alone in 2004. However, prescribing the appropriate dosage of Warfarin for each patient can be challenging due to **significant individual variability**. Incorrect dosages can result in **severe consequences**, including dangerous bleeding or inadequate prevention of blood clots. While various approaches, such as pharmacogenetic and clinical dosing algorithms, have been developed to determine the initial dosage, they still **rely on a trial-and-error procedure**, which can lead to adverse effects.

To address this challenge, this project aims to apply **multi-armed bandit algorithms** to predict the correct dosage of Warfarin without relying on a trial-and-error procedure. Specifically, the project investigates the performance of linear bandit algorithms, demonstrating that **LinUCB outperforms both the fixed and clinical dosing baselines**. We also investigate alternative model formulations and assess performance.

Models

Benchmark Mo

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LinUCB with Di

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Default Final Project
stimation of the Warfarin Dos

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odels

benchmark models against which we performance. The first is the fixed dose simply assigns every patient a medium d is the clinical dosing algorithm, a simple culates the square root of weekly dose as a patient covariates:

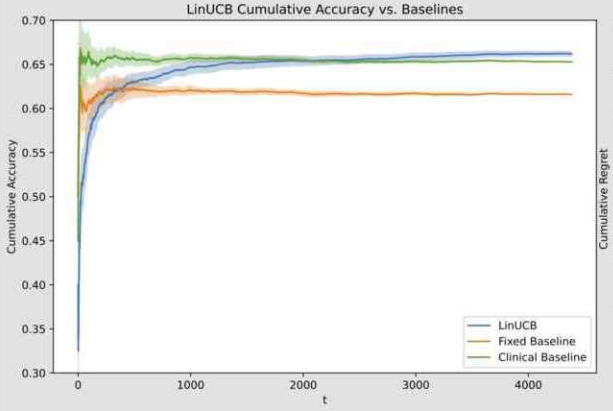
Age + 0.0118 ∗ Height (cm) + 0.0134 ∗ Weight (kg)
.4060 ∗ Black + 0.0443 ∗ Missing or mixed race + 1.2799
tus − 0.5695 ∗ Amiodarone status

isjoint Linear Models

dit algorithm is LinUCB with disjoint linear Li et al. (2010). In this model, the optimal lected based on a linear function of the eristics plus an optimism term to ensure tion. In the below equations, D refers to the

Results

We find that LinUCB significantly outperfo baseline, both in terms of both cumula cumulative expected regret. The resulting perf follows, with the shaded regions correspondi intervals over the 20 different random patient



We also go on to find that our extensio

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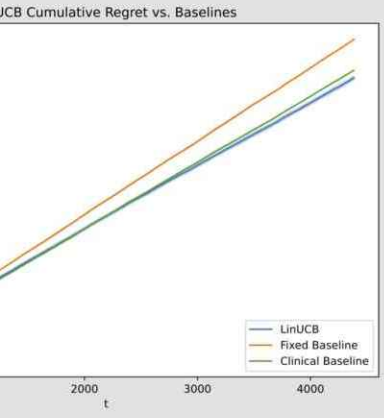

on models, namely

Discussion & Conclusion

Our results show clear performance improvements when comparing bandit methods to both the fixed dose baseline and, in the case of LinUCB, to the clinical dosing algorithm as well. This clearly demonstrates **the power of bandit methods** for Warfarin dose assignment and suggests that such methods should be **further explored** to achieve better patient outcomes.

However, there is one key caveat to these results: while **LinUCB outperforms the clinical dosing** algorithm by the end of the "online" training period, **it takes nearly 2000 patients** before its performance truly matches that of the clinical dosing algorithm. As a result, if this were a truly online setting, **several of those patients may have received a lower quality of care** than if the clinical dosing algorithm had been applied. This raises **ethical considerations** regarding potential harm to patients used in training bandit methods, particularly **for healthcare applications**. This suggests that **some degree of offline learning**, such as what

Data

This project leverages a publicly available patient dataset collected by PharmGKB. Comprising of 5528 patients drawn from studies across 9 countries, this dataset includes optimal patient-specific warfarin doses, as well as patient features such as gender, race, height, weight, medical history, genotypes, and phenotypes.

There are, however, a significant number of entries for which data is missing. We impute missing values of VKORC1, a genotype feature, based on the algorithm provided in the appendix to the dataset (I.W.P, 2009). The final set of features that we consider are age, height, weight, race, enzyme inducer status, amiodarone use, VKORC1, and CYP2C9 (another genotype feature, for which an imputation algorithm is not provided). We then drop all observations for which any of these features are null while treating unknown values of VKORC1 and CYP2C9 as a separate feature class. The result leaves us with 4386 observations with full data.

In order to handle these categorical genotypic features, we employ one-hot encoding, constructing a dummy variable for each class membership. We then drop one such dummy variable from each group and include an intercept in our feature space, in keeping with standard practice for linear models. The end result is a dataset with 4386 observations and 23 features.

The label, which we try to predict, is given by the correct therapeutic dose of warfarin, which we discretize into 3 bins corresponding to "*low*", "*medium*", and "*high*".

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Supervised Line

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$$\arg\max_{a \in \mathcal{A}_t} \left(x_{t,a}^{\top} \widehat{\boldsymbol{\theta}}_a + \alpha \sqrt{x_{t,a}^{\top} \boldsymbol{A}_a^{-1} x_{t,a}} \right)$$

$$+ I_d$$

mpling

it algorithm is Thompson Sampling, applied ndits with linear payoffs, based on Agrawal his algorithm works by posterior sampling, ple the linear parameter vector from a dating normal distribution, We deviate from implementation by giving each arm a parameters, thereby making it a disjoint LinUCB.

$$t) = I_d + \sum_{\tau=1}^{t-1} b(\tau) b(\tau)^T \, 1\{a_\tau = a\}$$

$$= B_a(t)^{-1} \left(\sum_{\tau=1}^{t-1} b(\tau) r(\tau) 1\{a_\tau = a\} \right)$$

$$\tilde{\mu}_a(t) \sim \mathcal{N}(\hat{\mu}_a(t), v^2 B_a(t)^{-1})$$

$$a_t = arg\max_a b^T(t) \tilde{\mu}_a(t)$$

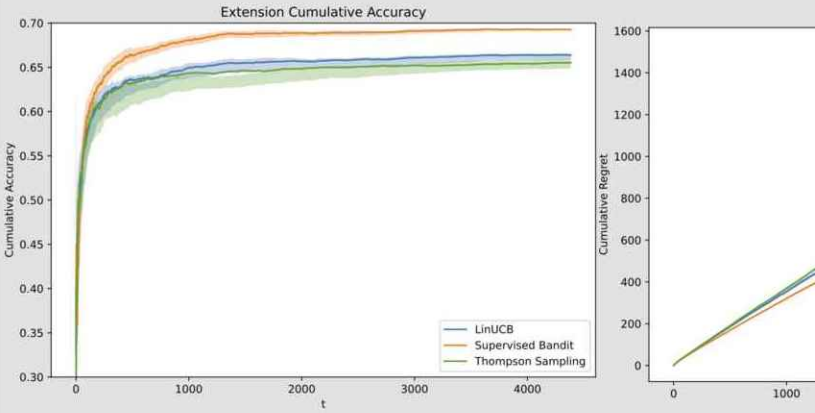
ear Bandit

n is a supervised linear bandit, which trains ed on all prior observed true Warfarin doses, ndard binary reward. By utilizing this extra model should achieve better performance ed and will set a kind of upper bound on the ear bandit models.

$$\hat{\theta}_t = (X_t^T X_t)^{-1} X_t^T Y_t$$

$$_{-1} = \arg\max_{a \in \{0,1,2\}} ||a - x_{t+1}^T \hat{\theta}_t||$$

supervised linear regression "bandit" and T achieve good performance:



We can see that Thompson Sampling appear performance to LinUCB (within error). As expe linear "bandit" achieves significantly higher regret compared to both models. This is unsur access to the true treatment applied to past pat reward, which amounts to just a bir correct/incorrect treatment.

References

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L. Li, W. Chu, J. Langford, and R. E. Schapire *Proceedings of the 19th internation*

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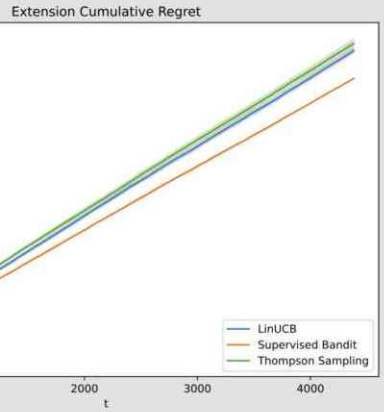

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we have performed in this project, is necessary prior to the rollout of a bandit algorithm in such contexts.

Future

The key direction of future research in this project is to investigate **further implementations of linear bandit models** to attempt to close the performance gap between our current optimal implementation, **LinUCB, and the supervised linear bandit**. While the latter's performance presents an upper bound on the potential performance of linear bandit models and likely **cannot be replicated** by a model that observes only binary rewards, the existing gap suggests that **other model formulations may be able to provide better performance.**

Possible candidates that we have not tested in this project include **robust algorithms or regularized linear models.**

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