Kernel Assisted Learning for Personalized Dose Finding

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ABSTRACT
An individualized dose rule recommends a dose level within a continuous safe dose range based on patient level information such as physical conditions, genetic factors and medication histories. Traditionally, personalized dose finding process requires repeating clinical visits of the patient and frequent adjustments of the dosage. Thus the patient is constantly exposed to the risk of underdosing and overdosing during the process. Statistical methods for finding an optimal individualized dose rule can lower the costs and risks for patients. In this article, we propose a kernel assisted learning method for estimating the optimal individualized dose rule. The proposed methodology can also be applied to all other continuous decision-making problems. Advantages of the proposed method include robustness to model misspecification and capability of providing statistical inference for the estimated parameters. In the simulation studies, we show that this method is capable of identifying the optimal individualized dose rule and produces favorable expected outcomes in the population. Finally, we illustrate our approach using data from a warfarin dosing study for thrombosis patients.

CCS CONCEPTS
• Mathematics of computing → Kernel density estimators;
  Probabilistic inference problems; Nonparametric statistics; Hypothesis testing and confidence interval computation; Multivariate statistics; Computing methodologies → Kernel methods;
  Model development and analysis; Q-learning; Applied computing → Mathematics and statistics; Health care information systems; Decision analysis; Theory of computation → Sequential decision making.

KEYWORDS
Individualized dose rules, Kernel estimation, Personalized medicine, Value function.
patients, from 10mg to 100mg per week [4]. Incorrect dosages contribute largely to the adverse effects of warfarin usage. Underdosing will fail to alleviate symptoms in patients and overdosing will lead to catastrophic bleeding. In this case, an individualized dose rule, where a dose level is suggested within a continuous safe dose range according to each individual’s physical conditions, would be better at tailoring to patient heterogeneity in drug response. Several methods have been proposed for finding optimal individualized dose rules. One way of extending existing methods to the continuous dose case is to discretize the dose levels. Laber and Zhao [11] proposed a tree-based method and turned the problem into a classification problem by dividing patients into subgroups and assigning a single dose to each subgroup. Chen et al. [2] extended the outcome weighted learning method [27] from binary treatment settings to ordinal treatment settings. However, in cases where patient responses are sensitive to dose changes, a discretized dose rule with a small number of levels will fail to provide dose recommendations leading to optimal clinical results. On the other hand, a discretized dose rule with a large number of levels may result in limited observations within each subgroup, and thus may be at risk of overfitting.

Alternatively, Rich et al. [15] extended the Q-learning method by modeling the interactions between the dose level and covariates with both linear and quadratic terms in doses. However, such a parametric approach is sensitive to model misspecification and the estimated individualized dose rule might be far away from the true optimal dose rule. In addition, it cannot be guaranteed that the estimated optimal dose falls into the safe dose range. More recently, Chen et al. [1] extended the outcome weighted learning method proposed by Zhao et al. [27] and transformed the dose-finding problem into a weighted regression with individual rewards as weights. The optimal dose rule is then obtained by optimizing a non-convex loss function. This method is robust to model misspecification and has appealing computational properties, however, the associated statistical inference for the estimated dose rule is challenging to determine. In this article we propose a kernel assisted learning method to infer the optimal individualized dose rule in a manner which enables statistical inference. Our proposed method can be viewed as a direct value search method. Specifically, we first estimate the value function with a kernel based estimator. Then we search for the optimal individualized dose rule within a prespecified class of rules where the suggested doses always lie in the safe dose range. This method is robust to model misspecification and is applicable to data from both randomized trials and observational studies. We establish the consistency and asymptotic normality of the estimated parameters in the obtained optimal dose rule. In particular, the asymptotic covariances of the estimators is derived based on nontrivial calculations of the expectation of a U-statistic.

The remainder of the article is organized as follows. In Section 2, we present the problem setting and our proposed method. The theoretical results of the estimated parameters are established in Section 3. In Section 4, we demonstrate the empirical performance of the proposed method via simulations. In Section 5, the proposed method is further illustrated with an application to a warfarin study. Some discussions and conclusions are given in Section 6. Proofs of the theoretical results are provided in the appendix.

2 METHOD

2.1 Problem Setting

The observed data consist of $n$ independent and identically distributed observations $\{(X_i, A_i, Y_i)\}_{i=1}^n$, where $X_i \in \mathcal{X}$ is a $d$ dimensional vector of covariates for the ith patient, $A_i \in \mathcal{A}$ is the dose assigned to the patient with $\mathcal{A}$ being the safe dose range, and $Y_i \in \mathbb{R}$ is the outcome of interest. Without loss of generality, we assume that larger $Y$ means better outcome. Let $\pi(X)$ denote an individualized dose rule, which is a deterministic mapping function from $\mathcal{X}$ to $\mathcal{A}$. To define the value function of an individualized dose rule, we use the potential outcome framework [17]. Specifically, let $Y^*(a)$ be the potential outcome that would be observed when a dose level $a \in \mathcal{A}$ is given. Define the value function as the expected potential outcome in the population if everyone follows the dose rule $\pi$, i.e. $V(\pi) = E[Y^*(\pi(X))]$. The optimal individualized dose rule is defined as $\pi^{opt} = \arg \max \ V(\pi)$.

In order to estimate the value function from the observed data, we need to make the following three assumptions similar to those adopted in the causal inference literature [16]. First, we assume $Y = \int_{\mathcal{A}} \delta(\pi = a) Y^*(a) da$, where $\delta(\cdot)$ is the Dirac delta function. This corresponds to the stable unit treatment value assumption (also known as the consistency assumption). It assumes that the observed outcome is the same as the potential outcome had the dosage given to the patient be the actual dose. This assumption also implies that there is no interference among patients. Second, we assume that the potential outcomes $\{Y^*(a) : a \in \mathcal{A}\}$ are conditionally independent of $A$ given $X$, which is also known as the no unmeasured confounders assumption. Third, we assume that there exists a $c > 0$ such that $p(A = a | X = x) \geq c$ for all $a \in \mathcal{A}, x \in \mathcal{X}$, where $p(a|x)$ is the conditional density of $A = a$ given $X = x$. This is a generalization of the positivity assumption for continuous dosing. Under these assumptions, we can show that $V(\pi)$ can be estimated with the observed data:

$$V(\pi) = E[Y^*(\pi(X))] = EX\{E[Y^*(\pi(X))|X]\} = EX\{E[Y^*(\pi(X)|A = \pi(X), X]\}$$

The second equation above is based on the basic property of conditional densities. The third equation above is valid because of the no unmeasured confounder assumption. The fourth equation is based on the consistency assumption. The positivity assumption ensures that the right side of the last equation can be estimated empirically. In the next section, we will propose a consistent estimator for $V(\pi)$ based on kernel smoothing.

2.2 Method

To estimate the optimal IDR, we first estimate $V(\pi)$ with a kernel based estimator $\hat{V}(\pi)$ and then estimate $\pi^{opt}$ by directly maximizing the estimated value function $\hat{V}(\pi)$. We search for the optimal individualized dose rule within a class of dose rules of the form: $\pi_\beta(x) = \pi(x; \beta) \in \mathcal{G}$, where $\mathcal{G} = \{g(\beta^T x), \beta \in \mathbb{R}^d\}$, and $g : \mathbb{R} \rightarrow \mathcal{A}$ is a predefined link function to ensure that the suggested dosage is within the safe dose range. Thus $\pi^{opt} = \arg \max_{\pi \in \mathcal{G}} \hat{V}(\pi)$.

Notice that $\pi^{opt}$ is an estimator of the optimal IDR within $\mathcal{G}$: $\pi^{opt}_\beta = \arg \max_{\pi \in \mathcal{G}} \hat{V}(\pi) = \pi_\beta^*$, where $\pi^*_\beta = \arg \max_{\pi \in \mathcal{G}} \hat{V}(\pi)$. If the true optimal IDR lies in $\mathcal{G}$, then the proposed $\pi^{opt}_\beta(X) = \pi^{opt}$.
To see this more clearly, we illustrate with a toy example. If the true model for \( E(Y | A, X) \) takes the form: \( E(Y | A, X) = \mu(X) + Q(A - g(\beta^T X))X \), where \( \mu(X) \) is an unspecified baseline function, \( H(X) \) is a non-negative function and \( Q(\cdot) \) is a unimodal function which is maximized at 0, then \( E(Y | A, X) \) is maximized at dose level \( A = g(\beta^T x) \) for patients with covariates \( X = x \). Thus, the true optimal individualized dose rule is:

\[
\pi^{opt}(X) = \arg \max \pi \ E(Y | A = \pi(X), X) \\
= \arg \max \pi E_X \left[ E(Y | A = \pi(X), X) \right] \\
= \arg \max \pi E_X \left[ \mu(X) + Q(\pi(X) - g(\beta^T X))H(X) \right] \\
= g(\beta^T X) \in \mathcal{G}.
\]

The last equation above is true because \( Q(\pi(X) - g(\beta^T X))H(X) \) is maximized at \( g(\beta^T X) \) for each \( X \in X \). If a unique maximizer of \( V(\pi) \) exists, then

\[
\beta^* = \arg \max \beta \ E_X \left[ \mu(X) + Q(\pi(X) - g(\beta^T X))H(X) \right] = \hat{\beta}.
\]

Therefore, \( \pi^{opt}_\beta = g(\beta^T X) = \pi^{opt} \). Notice that if, \( \pi^{opt} \neq \pi \), then \( \pi^{opt}_\beta \neq \pi^{opt} \). However, \( \pi^{opt} \) is still of interest as long as the form of \( \mathcal{G} \) is flexible enough, because it maximizes the value function among this set of treatment rules, \( \beta^* \) can be estimated using \( \hat{\beta} = \arg \max \tilde{V}(\pi), \) and the optimal IDR within \( \mathcal{G} \) can be thus estimated with \( \pi^{opt}_\hat{\beta} = \pi(X; \hat{\beta}) \). Notice that we do not need any model assumption on the form of the conditional expectation \( E(Y | A, X) \) to apply this method.

Next, we propose a kernel based estimator for the value function. Let

\[
M_\beta(\pi) = V(\pi) = \int_{x \in X} m(x, g(\beta^T x)) f(x) dx,
\]

where \( m(x, a) = E(Y | X = x, A = a) \) and \( f(x) \) is the marginal density of \( X \). Thus, \( \beta^* = \arg \max_\beta M(\beta) \). The function \( m(x, g(\beta^T x)) \) is estimated using the Nadaraya-Watson method given:

\[
\hat{m}(x, g(\beta^T x)) = \frac{1}{n} \sum_{i=1}^{n} \frac{1}{h_x} K_d \left( \frac{x - X_i}{h_x} \right) \frac{1}{h_\nu} K \left( \frac{g(\beta^T x) - A_i}{h_\nu} \right),
\]

where \( K(\cdot) \) is a univariate kernel function and \( K_d(\cdot) \) is a \( d \) dimensional kernel function. Here, \( h_x \) and \( h_\nu \) are bandwidths that go to 0 as \( n \to \infty \). Note that for simplicity of notation, we use the same bandwidth for all dimensions of \( X \) here. In practice, we can use different bandwidths for different dimensions of \( X \) to increase the efficiency of the estimation. Moreover, the marginal density of \( X \) is estimated by \( f(x) = (1/n) \sum_{i=1}^{n} K_d((x - X_i)/h_x)/h_x \). The estimated value function can thus be written as:

\[
M_n(\beta) = \int_X \frac{1}{n} \sum_{i=1}^{n} \frac{1}{h_x} K_d \left( \frac{x - X_i}{h_x} \right) \frac{1}{h_\nu} K \left( \frac{g(\beta^T x) - A_i}{h_\nu} \right) \left[ \frac{1}{h_\nu} \sum_{i=1}^{n} \frac{1}{h_x} K_d \left( \frac{x - X_i}{h_x} \right) \right] dx.
\]

Then \( \beta^* \) is estimated with \( \hat{\beta}_n = \arg \max_{\beta \in \Theta} M_n(\beta) \), where \( \Theta \) is a compact subset of \( \mathbb{R}^d \) containing \( \beta^* \).

2.3 Computational Details

To implement the proposed method, the R package optimr() is used for optimization of the objective function. The integral in \( M_n(\beta) \) is estimated by taking the average of \( q \) grid points in the covariate space. In our implementation, we chose \( q = 3000. \) In order to find the global maximizer of \( M_n(\beta) \), we start optimization from \( d \) different initial points \( \{(1, 0, \ldots, 0), (0, 1, 0, \ldots, 0), \ldots, (0, 0, 0, 1)\} \) and choose the one that leads to the maximal objective function value. Denote the maximizer as \( \hat{\beta}_n \). When there is only one continuous covariate included, following the theoretical rate of the bandwidth parameters, the bandwidths are chosen as \( h_x = C_x sd(X)n^{-1/4.5}, h_\nu = C_\nu sd(A)n^{-1/4.5} \), where \( C_x \) and \( C_\nu \) are constants between 0.5 and 3.5.

When the covariates consist of both continuous variables and categorical variables, the categorical variables are stratified for estimation of the value function. Specifically, assume that \( X = (X_1^T, X_2^T)^T \in X \), where \( X_1 \in C \) is a \( d_1 \) dimensional vector of continuous variables and \( X_2 \in \mathcal{D} \) is a \( d_2 \) dimensional vector of categorical variables. The form of \( M_n(\beta) \) then becomes:

\[
M_n(\beta) = \sum_{x_2 \in \mathcal{D}} \int_{x_1 \in C} \frac{1}{n} \sum_{i=1}^{n} Y_i K(X_i, X_1) \frac{1}{h_x} K \left( \frac{g(\beta^T x_1) - A_i}{h_\nu} \right) \frac{1}{h_\nu} \sum_{i=1}^{n} K(X_i, X_1) dx_1,
\]

where \( x = (x_1^T, x_2^T)^T, X_1 = (X_{11}^T, X_{12}^T)^T, K(X_i, X_1) = (1/h_{d_1} K_d) \{ (x_1 - X_{11})/h_x \} I(X_{12} = x_2) \).

The R code for the proposed method can be downloaded at: https://drive.google.com/drive/folders/1eZ3VEtudZDHZd81QxfQTHgTc8GPfZdf?usp=sharing

3 THEORETICAL RESULTS

In this section, we establish the asymptotic properties of \( \hat{\beta}_n \). To prove these results, we need to make the following assumptions. In the following equations, \( f(x), f(x) \) and \( f(x) \) denote the first, second and third derivatives of the function \( f \) with respect to \( x; k_{0,2} = \int_{\mathbb{R}} K^2(v) dv \) and \( k_{0,2} = \int_{\mathbb{R}} K^2(v) dv \).

Assumption 1. 1 Assume that \( \tilde{K}(v), \hat{K}(v) \) and \( \tilde{K}(v) \) exist for \( v \in V \), where \( V \) is a subset of \( \mathbb{R} \). For \( h \to 0^+ \) as \( n \to \infty \) and constants \( l_a \) such that \( l < 0 < u \),

\[
\int_{[l/h_a, u/h_a]} v \tilde{K}(v) dv = O(h^2), \int_{[l/h_a, u/h_a]} v \hat{K}(v) dv = O(h), \int_{[l/h_a, u/h_a]} v \tilde{K}(v) dv = O(h^2), \int_{[l/h_a, u/h_a]} v \hat{K}(v) dv = O(h), \int_{[l/h_a, u/h_a]} v \tilde{K}(v) dv = O(h^2), \int_{[l/h_a, u/h_a]} v \hat{K}(v) dv = O(h^2).
\]


\[ O(h^2), \int_{[l/h,u/h]} i \gamma_v K^2(v) \, dv = \hat{\kappa}(0) - O(h^2), \int_{[l/h,u/h]} i \gamma_v K(v) \, dv = O(h), \int_{[l/h,u/h]} i \gamma_v K(v) \, dv = 2 - O(h^2), \int_{[l/h,u/h]} i \gamma_v K(v) \, dv = O(h^2), \int_{[l/h,u/h]} i \gamma_v K(v) \, dv = O(1). \]

Assumption 2. The function \( M(\beta) = V(\pi_\beta) \) has a unique maximizer \( \beta^* \).

Assumption 3. The function \( m(x,a) \) is uniformly bounded. The joint density function of \( X \) and \( A, f(x,a) \), is uniformly bounded away from 0. In addition, the first, second, third and fourth order derivatives of \( m(x,a) \) and \( f(x,a) \) with respect to \( x \) and \( a \) are and are uniformly bounded almost everywhere.

Assumption 4. The covariate \( X \) has bounded first, second and third moments.

Assumption 5. The function \( g(\cdot) \) is thrice differentiable almost everywhere and the corresponding derivatives, \( g_1(\cdot), g_2(\cdot), g_3(\cdot) \) are bounded almost everywhere.

Assumption 1 can be satisfied by most commonly used kernel functions such as the Gaussian kernel function and all sufficiently smooth bounded kernel functions. Assumption 2 is an identifiability condition for \( \beta^* \). Assumptions 3–5 ensure the existence of the limit of the expectation of \( M_n(\beta) \) and the existence of the covariance matrix of the limiting distribution. In the following two theorems, we establish the consistency and asymptotic normality of \( \hat{\beta}_n \), respectively.

Theorem 3.1. Under assumptions 1–3, for \( h_x, h_a \) satisfying \( nh_x^2 h_a^2 \to \infty \) as \( n \to \infty \), we have \( \sup_{\beta \in \Theta} |M_n(\beta) - M(\beta)| \to 0 \) in probability, where \( \Theta \) is a compact region containing \( \beta^* \). Thus, \( \hat{\beta}_n = \arg \max_{\beta \in \Theta} M_n(\beta) \) converge in probability to \( \beta^* \).

Theorem 3.2. Under assumptions 1–5, for \( h_x, h_a \) satisfying \( nh_x^2 h_a^2 \to \infty \) as \( n \to \infty \), we have

\[
(nh_x^2 h_a^2)^{1/2} (\hat{\beta}_n - \beta^*) \to N \{ 0, D(\beta^*)^{-1} \Sigma_\beta(\beta^*) D(\beta^*)^{-1} \}
\]

in distribution as \( n \to \infty \), where

\[
D(\beta^*) = \int_x m_{ax} \{ x, g(\beta^T x) \} g_2^2(\beta^T x) + m_a \{ x, g(\beta^T x) \} g_1(\beta^T x) \} f(x)xx^T \, dx,
\]

\[
\Sigma_\beta(\beta^*) = \int_x \left[ g_2^2(\beta^T x) xx^T \kappa_{0,2}, \kappa_{0,2} f^2(\beta^T x) \left[ m_2 \{ x, g(\beta^T x) \} - m_1 \{ x, g(\beta^T x) \} f(x, g(\beta^T x)) \right] \right] \, dx,
\]

and \( m_a(x,a) = \partial m(x,a)/\partial a, m_{ax}(x,a) = \partial^2 m(x,a)/\partial a^2, m_2(x,a) = E(Y^2 \mid X = x, A = a). \)

Proofs of the above theorems are based on theory for kernel density estimators [18] and M-estimation [10]. Details of proofs are given in the appendix. Note that the convergence rate is slower then \( n^{1/2} \) due to the kernel estimation of the value function.

### 4 SIMULATION STUDIES

In this section, we conduct some simulations to show the capability of our proposed method in identifying the optimal individualized dose rule. We first simulate some simple settings with only one covariate. \( X \) is generated randomly from the standard normal distribution. \( A \) is generated from the uniform distribution on \([0,1]\). We generate \( A \) and \( X \) independently to mimic a randomized dose trial where a random dose from the safe dose range is assigned to each patient. The optimal dose rule is \( n_{opt}(X) = g(\tilde{\beta}_0 + \tilde{\beta}_1 X) \), where \( g(s) = 1/(1 + \exp(-s)) \). \( Y \) is generated from a normal distribution with mean \( m(A,X) \) and standard deviation 0.5, where \( m(A,X) = \mu(X) - 10(A - n_{opt}(X))^2 \). We use two different baseline functions for \( \tilde{\mu}(X) \) and two different sets of \((\tilde{\beta}_0, \tilde{\beta}_1)\) as shown in Table 1. The sample sizes are \( n = 400 \) and \( n = 800 \) and each setting is replicated 500 times.

The average bias and the standard deviation of the estimated parameters from 500 simulations are summarized in the first half of Table 2. The estimated parameters were close to the true parameters. The third column shows the average of the standard errors estimated with the covariance function formula derived in Theorem 3.2 (see appendix for details). 95% confidence intervals were calculated with the estimated standard errors. The coverage probabilities are shown in the table. From the result, we can see that the bias and standard deviation of the estimated parameters decreased with larger sample sizes. The coverage probabilities of the confidence intervals were close to 95%, supporting the convergence results given in Section 3.

We also study the performance of our method when the training data are from observational studies, where the doses given to the patients may depend on the covariates \( X \). The simulation settings are the same as settings 1–4 except that \( A \) is generated from the distribution beta \( \{ 2 \exp(\tilde{\beta}_0 + \tilde{\beta}_1 X) \} \). The results are summarized in the second half of Table 2. The proposed method was still capable of giving good estimates of the parameters and the coverage of the confidence intervals were close to 95%. These simulation implies that the proposed method performs well with data from both randomized trials and observational studies.

Under settings 1–4, we compare our method with linear based O-learning (LOL) and kernel based O-learning (KOL) proposed in Chen et al. [1] and a discretized dose rule estimated using Q-learning. For discretized Q-learning, we divide the safe dose range into \( 10 \) equally spaced intervals: \( A = A_1 \cup \ldots \cup A_{10} \) and create an indicator variable for each of the dose intervals \( I = \{ I_1, I_2, \ldots, I_{10}\} \), where \( I_j = I \in A_j \), \( j = 1, \ldots, 10 \). The covariates included in the regression models are \( (X^2, I_1, I_X, I_X^2) \). To this end, an optimal dose range is selected for each individual and the middle point of the selected interval is suggested to the patient. The results from

| Table 1: Summary of simulation settings |
|---------------------------------------|
| No baseline | With baseline |
| \( \tilde{\beta}_0 = 0, \tilde{\beta}_1 = 0.5 \) | \( \tilde{\mu}(X) = 0 + 0.5 \cos(2\pi X) \) |
| Setting 1 | Setting 3 |
| \( \tilde{\beta}_0 = 0, \tilde{\beta}_1 = 1 \) | \( \tilde{\mu}(X) = 1 + 0.5 \cos(2\pi X) \) |
| Setting 2 | Setting 4 |
Warfarin is a widely used anticoagulant for prevention of thromboembolism and thromboembolism. Although highly efficacious, dosing for warfarin is known to be challenging because of the narrow therapeutic index and the large variability among patients [8]. Overdosing of warfarin leads to bleeding and underdosing diminishes the efficacy of the medication. The international normalized ratio (INR) measures the clotting tendency of the blood. An INR between 2–3 is considered to be safe and efficacious for patients. Typically, the warfarin dosage is decided empirically: an initial dose is given based on the population average, and adjustments are made in the subsequent weeks while the INR of the patient is being tracked. A stable dose is decided in the end to achieve an INR of settings 1–4. The dosing process may take weeks to months, during which the patient is constantly at risk of bleeding or under-dosing. Therefore, a quantitative method for warfarin dosing will greatly decrease the time, cost and risks for patients.

The following analysis uses the warfarin dataset collected by Consortium [4]. In the original paper, a linear regression was used to predict the stable dose using clinical results and pharmacogenetic information, including age, weight, height, gender, race, two kinds of medications (Cytochrom P450 and Amiodarone), and two genotypes (CYP2C9 genotype and VKORC1 genotype). This prediction method is based on the assumption that the stable doses received by the patients are optimal. However, later studies showed that the suggested doses by the International Warfarin Pharmacogenetic Consortium are suboptimal for elderly people, implying that the optimal dose assumption might not be valid [1].

We apply our proposed method to this dataset to estimate the optimal individualized dose rule for warfarin. Instead of using only the data of the patients with stabilized INR, we include all patients who received weekly doses between 6 mg to 95 mg. The medication information is missing for half of the observations and is therefore excluded from our analysis. Observations which are missing in the subsequent weeks while the INR of the patient is being tracked. A stable dose is decided in the end to achieve an INR of 2–3 [8].

5 WARFARIN DATA ANALYSIS

Warfarin is a widely used anticoagulant for prevention of thrombosis and thromboembolism. Although highly efficacious, dosing for warfarin is known to be challenging because of the narrow therapeutic index and the large variability among patients [8]. Overdosing of warfarin leads to bleeding and underdosing diminishes the efficacy of the medication. The international normalized ratio (INR) measures the clotting tendency of the blood. An INR between 2–3 is considered to be safe and efficacious for patients. Typically, the warfarin dosage is decided empirically: an initial dose is given based on the population average, and adjustments are made in the subsequent weeks while the INR of the patient is being tracked. A stable dose is decided in the end to achieve an INR of 2–3 [8].

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### Table 2: Simulation results from 500 replicates for randomized trials and observational studies.

| Randomized trials | $\hat{\beta}_{c,0}$ | $\hat{\beta}_{c,1}$ | $\hat{\beta}_{f,0}$ | $\hat{\beta}_{f,1}$ |
|-------------------|-------------------|-------------------|-------------------|-------------------|
| n Bias SD SE CP   |                   |                   |                   |                   |
| S1 400 2.5 46.6 47.5 95.6 |                   |                   |                   |                   |
| 800 2.4 33.7 33.4 95.8 |                   |                   |                   |                   |
| S2 400 2.1 52.2 54.4 95.6 |                   |                   |                   |                   |
| 800 1.5 39.1 38.1 93.8 |                   |                   |                   |                   |
| S3 400 2.7 54.1 55.7 95.2 |                   |                   |                   |                   |
| 800 1.6 38.8 39.3 95.0 |                   |                   |                   |                   |
| S4 400 2.4 61.8 63.4 95.4 |                   |                   |                   |                   |
| 800 -1.5 44.4 44.3 94.6 |                   |                   |                   |                   |

| Observational studies | $\hat{\beta}_{c,0}$ | $\hat{\beta}_{c,1}$ | $\hat{\beta}_{f,0}$ | $\hat{\beta}_{f,1}$ |
|-----------------------|-------------------|-------------------|-------------------|-------------------|
| n Bias SD SE CP       |                   |                   |                   |                   |
| S1 400 13.9 80.5 82.4 96.0 |                   |                   |                   |                   |
| 800 8.5 47.3 47.0 94.6 |                   |                   |                   |                   |
| S2 400 21.9 83.3 88.1 96.4 |                   |                   |                   |                   |
| 800 17.8 63.4 60.9 93.0 |                   |                   |                   |                   |
| S3 400 13.4 89.4 90.2 95.6 |                   |                   |                   |                   |
| 800 9.0 53.1 50.6 93.0 |                   |                   |                   |                   |
| S4 400 21.6 91.3 97.1 96.2 |                   |                   |                   |                   |
| 800 20.3 71.2 67.6 93.2 |                   |                   |                   |                   |

Note: * columns are in 10^-3 scale.

Note: SD refers to the standard deviation of the estimated parameters from 500 replicates. SE refers to the mean of the estimated standard errors calculated using the estimated standard errors.

### Table 3: Value estimate $V(\hat{x})$ from 500 simulations in settings 1-4.

| Randomized trials | n | DQ | LOL | KOL | KAL |
|-------------------|---|----|-----|-----|-----|
| S1 400 -38.1(1.9) | -7.7(7.0) | -16.5(8.2) | -2.7(2.7) |
| 800 -32.7(0.9) | -3.9(3.7) | -9.3(4.3) | -1.9(1.8) |
| S2 400 -33.9(1.3) | -18.1(10.5) | -31.7(12.5) | -3.3(3.7) |
| 800 -20.0(0.8) | -15.6(7.5) | -20.4(7.4) | -1.9(1.8) |
| S3 400 -41.6(11.4) | -8.5(14.1) | -17.2(14.2) | -3.7(12.4) |
| 800 -61.2(11.5) | -4.3(12.1) | -10.0(12.7) | -2.4(11.7) |
| S4 400 -52.5(11.9) | -21.3(17.7) | -33.3(17.4) | -4.2(12.5) |
| 800 -23.3(11.9) | -17.8(14.5) | -22.4(13.9) | -2.4(11.7) |

Note: DQ refers to discretized Q-learning. LOL refers to linear O-learning. KOL refers to kernel based O-learning. KAL refers to kernel assisted learning.

All columns are in 10^-3 scale. For settings 3 and 4, the numbers in the table are the value estimate $V(\hat{x}) - 1$ for the purpose of comparison with the first two settings.

### Table 3: Value estimate $V(\hat{x})$ from 500 simulations in observational studies.

| n | DQ | LOL | KOL | KAL |
|---|----|-----|-----|-----|
| S1 400 -29.5(1.2) | -7.4(6.3) | -15.6(7.7) | -8.1(8.0) |
| 800 -24.4(0.9) | -5.5(4.3) | -10.3(5.3) | -3.1(3.1) |
| S2 400 -16.0(7.6) | -14.1(6.6) | -21.3(9.7) | -8.2(8.3) |
| 800 -32.0(1.1) | -12.8(4.7) | -12.2(4.5) | -4.4(4.4) |
| S3 400 -29.1(11.6) | -8.1(13.5) | -11.7(14.6) | -9.8(15.7) |
| 800 -34.2(11.8) | -6.2(12.4) | -11.2(13.3) | -3.5(12.0) |
| S4 400 -83.8(13.8) | -14.7(13.0) | -20.7(15.8) | -10.0(15.8) |
| 800 -34.1(11.3) | -13.5(12.1) | -11.2(12.3) | -5.1(12.2) |

Note: SD refers to the standard deviation of the estimated parameters from 500 replicates. SE refers to the mean of the estimated standard errors calculated using the estimated standard errors.

Note: The worst case Monte Carlo standard error for proportions is 1.3%.
other variables are removed from the dataset, resulting in a total of 3567 patients. The outcome variable is defined as \( Y_i = -(\text{INR}_i - 2.5)^2 \) for the \( i \)-th observation. Stratification of the categorical variables is needed for the kernel density estimation. In order to ensure that there are enough observations in each stratified group, we consider only categorical variables that are distributed comparatively even among different groups. In our analysis, we use three variables: height, gender and the indicator variable for VKORC1 of type AG. Before we apply the proposed method, we normalize all the variables by \( \bar{X}_{i,j} = (X_{i,j} - \bar{X}_j)/sd(X_j) \), where \( j = 1, 2, 3, i = 1, \ldots, n \). The process is repeated 200 times. The distribution of the estimated value of the suggested dose is shown in Fig. 3. The suggested individualized dose rule with our proposed method lead to better expected outcomes in the population compared to the other methods. The performance of the discretized Q-learning method was not stable as shown in the result. However, this result was only based on the three variables selected, while in reality, the two medications (Cytochrome P450 enzyme and Amiodarone) and the genotype CYP2C9 are also of significant importance in warfarin dosing. The computation complexity of our proposed method restricted its capability of handling higher dimensional problems.

Table 4: Estimated \( \hat{\beta} \) with warfarin data with kernel assisted learning

| Variable           | Estimated Parameter | SE  | p-value |
|--------------------|---------------------|-----|---------|
| Intercept          | -0.463              | 0.064 | 0.000   |
| Height             | -0.263              | 0.101 | 0.005   |
| Gender             | 0.268               | 0.134 | 0.023   |
| VKORC1.AG          | -0.4682             | 0.094 | 0.000   |

6 DISCUSSION AND CONCLUSION

The proposed kernel assisted learning method for estimating the optimal individualized dose rule provides the possibility of conducting statistical inference with estimated dose rules, thus providing insights on the importance of the covariates in the dosing process. In our simulation settings, our method was capable of identifying the optimal individualized dose rule when the optimal dose rule was inside the prespecified class of rules. In the warfarin dosing case, based on the three covariates selected, the suggested dose lead to better expected clinical result compared to the other methods. Application of the proposed methodology is not limited to optimal dose finding. This method can also be applied to any scenario where continuous decision making is desired.

The proposed method has several possible extensions. Notice that the form of the prespecified rule class can be extended to a link function with a nonlinear predictor \( g(\Psi(X)^T \beta) \) where \( \Psi(\cdot) = (\Psi_1(\cdot), \ldots, \Psi_3(\cdot))^T \) are some prespecified basic spline functions and \( \beta \in \mathbb{R}^c \). The accuracy of the approximated value function might also be improved by extending the multivariate kernel \( K_d(x/h_x)/h_x \) to \( |H|^{-1/2} K_d(H^{-1/2} x) \) [5].

One weakness of the proposed method is that the accuracy of the estimated value function is sensitive to the choice of bandwidth. The kernel density estimator in the denominator of \( M_d(\beta) \) might lead to large bias when the bandwidths are not properly chosen. As the dimension of \( X \) increases, the choice of the bandwidths is nontrivial. The criteria for choosing bandwidths needs to be studied further.
Figure 2: Empirical distribution of suggested doses of several methods for the warfarin dataset. Panel (a) presents the distribution of the original doses from the dataset, the distributions of the suggested doses using the kernel assisted learning (KAL), linear outcome-weighted learning (LOL) and kernel based outcome-weighted learning (KOl). Panel (b) presents the histogram of the suggested doses using discretized Q-learning.

Figure 3: Empirical distribution of the estimated value function over 200 repetitions for the warfarin dataset.

In the future, we are interested in variable selection when dealing with high dimensional data. Extensions to multi-stage dose finding problems is also of interest. Personalized Dose Finding is still a relatively new problem. With the complicated mechanisms of various diseases, there are many more problems to be tackled in this realm.

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A PROOF OF THEOREM 3.1

For simplicity of notation, let’s define $m_0(x, a) = \partial f(x, a)/\partial a$, $m_0(x, a) = \partial f(x, a)/\partial x$, $m_2(x, a) = \partial m_0(x, a)/\partial x$, $m_2(x, a) = \partial f(x, a)/\partial x$, $f_0(x, a) = \partial f(x, a)/\partial a$, $f_0(x, a) = \partial f(x, a)/\partial x$.

We write $M_0(\beta)$ as $\int_x A_0(x)C_n(x)dx$, where $A_0(x, \beta) = \frac{1}{\beta} \sum_{i=1}^n \frac{1}{h_x} K_1(\frac{X_i - x}{h_x}) K(\frac{\beta g(x)}{h_x})$, $B_0(x, \beta) = \frac{1}{\beta} \sum_{i=1}^n \frac{1}{h_x} K_2(\frac{X_i - x}{h_x}) K(\frac{\beta g(x)}{h_x})$, $C_n(x) = \frac{1}{\beta} \sum_{i=1}^n \frac{1}{h_x} K_1(\frac{X_i - x}{h_x}) K(\frac{\beta g(x)}{h_x})$, $M(\beta)$ can be written as $\int_x A(\beta)C(x)dx$, $A(\beta) = m(x, g(\beta^T x))$, $B(\beta) = f(x, g(\beta^T x))$ and $C(x) = f(x)$. Thus, $\sup_{\beta} [M_0(\beta) - M(\beta)] = \sup_{\beta} \left[ \int_x A_0(x)C_n(x) - A(\beta)C(x) \right] \leq \sup_{\beta} \left[ \int_x A_0(x)C_n(x) dx + \sup_{x} \left| \int_x A_0(x)C_n(x) - C(x) \right| \right] \leq \sup_{x} \left| \int_x A_0(x)C_n(x) dx \right| + \sup_{x} \left| \int_x C_n(x) - C(x) \right| dx$, where $A_n(x, a) = \frac{1}{\beta} \sum_{i=1}^n \frac{1}{h_x} K_2(\frac{X_i - x}{h_x}) K(\frac{a - \beta \hat{g}(x)}{h_x})$, $B_n(x, a) = \frac{1}{\beta} \sum_{i=1}^n \frac{1}{h_x} K_2(\frac{X_i - x}{h_x}) K(\frac{a - \beta \hat{g}(x)}{h_x})$, $A^*(x, a) = m(x, a) f(x, a)$, $B^*(x, a) = f(x, a)$.

It is trivial to prove that $\int_x C_n(x) - C(x) \leq 0$. Thus, under the boundedness of $m(x, a)$, we only need to show that $\int_x C_n(x) - C(x) \leq \sup_{x,a} \left[ f_n(x, a) - f(x, a) \right] = \sup_{x,a} \left[ f_n(x, a) - f(x, a) \right] \rightarrow 0$.

To prove the first equation, note that $\int_x C_n(x) - C(x) dx \leq \int_x C_n(x) dx = \sup_{x} \left[ f_n(x, a) - f(x, a) \right] = 2$. By the dominated convergence theorem, it suffices to show the uniform convergence of the kernel density estimate $C_n(x)$ to $C(x)$, which can be achieved according to Schuster (1969).
The uniform convergence of \( B^n_n(x, a) \) can be proved similarly. Thus, we can obtain \( \sup_{\beta \in \Theta} \left| M_n(x; \beta) - M(x; \beta) \right| \to 0 \).

By Theorem 2.10 of Kosorok (2008), we now obtain that \( \hat{\beta}_n \to \beta_0 \).

**B PROOF OF THEOREM 3.2**

Since \( \hat{\beta}_n \) and \( \beta^* \) are maximizers of \( M_n(\beta) \) and \( M(\beta) \), they are solutions of \( S_n(\beta) = 0 \) and \( S(\beta) = 0 \), where, \( S(\beta) = \partial M(\beta)/\partial \beta \) and \( S_n(\beta) = \partial M_n(\beta)/\partial \beta \). By Taylor expansion, we have

\[
S_n(\beta^*) + D_n(\beta)(\hat{\beta}_n - \beta^*) + \frac{1}{2}\left( \hat{\beta}_n - \beta^* \right)^T \frac{\partial^2}{\partial \beta \partial \beta^T} S_n(\beta)(\hat{\beta}_n - \beta^*)
\]

\[
= S_n(\beta^*) + \frac{1}{2}\left( \hat{\beta}_n - \beta^* \right)^T \frac{\partial^2}{\partial \beta \partial \beta^T} S_n(\beta^*) (\hat{\beta}_n - \beta^*)
\]

where \( \hat{\beta} \) is on the line segment connecting \( \hat{\beta}_n \) and \( \beta^* \),

\[
D_n(\beta) = \frac{\partial^2}{\partial \beta \partial \beta^T} M_n(\beta)/\partial \beta \partial \beta^T, D(\beta) = \frac{\partial^2}{\partial \beta \partial \beta^T} M(\beta)/\partial \beta \partial \beta^T.
\]

To prove the weak convergence of \( \hat{\beta}_n \), we can first prove that as

\[
n \to \infty:
\]

\[
(n h_n^2)^{1/2}\left\{ S_n(\beta^*) - S(\beta^*) \right\} \overset{d}{\to} N(0, \Sigma_0(\beta^*)), \tag{A.2}
\]

\[
D_n(\beta) - D(\beta) = o_p(1), \tag{A.3}
\]

\[
\frac{1}{2}\left( \hat{\beta}_n - \beta^* \right)^T \frac{\partial^2}{\partial \beta \partial \beta^T} S_n(\beta) (\hat{\beta}_n - \beta^*) = o_p(1). \tag{A.4}
\]

Then we obtain:

\[
(n h_n^2)^{1/2}(\hat{\beta}_n - \beta^*) = \left\{ D_n(\beta^*) + \frac{1}{2}\left( \hat{\beta}_n - \beta^* \right)^T \frac{\partial^2}{\partial \beta \partial \beta^T} S_n(\beta^*) \right\} (n h_n^2)^{1/2} S_n(\beta^*)
\]

\[
\overset{d}{\to} N(0, D(\beta^*))^{-1} \Sigma_0(\beta^*) D(\beta^*))^{-1}
\]

as \( n \to \infty \).

**B.1 PROOF OF EQUATION (A.2)**

To prove Equation (A.2), we first write \( S_n(\beta) \) as:

\[
S_n(\beta) = \frac{\partial M_n(\beta)}{\partial \beta} = \int_x A_n(x; \beta) B_n(x; \beta) - A_n(x; \beta) B_n(x; \beta) C_n(x) dx,
\]

where

\[
A_n(x; \beta) = \frac{\partial}{\partial \beta} A_n(x; \beta),
\]

\[
B_n(x; \beta) = \frac{\partial}{\partial \beta} B_n(x; \beta),
\]

\[
= \frac{1}{n} \sum_{i=1}^n X_i X_i K_{a h_n}(\frac{x_i - X_i}{h_n}) g(\beta^T x) x,
\]

\[
\hat{B}_n(x; \beta) = \frac{\partial}{\partial \beta} \hat{B}_n(x; \beta),
\]

\[
= \frac{1}{n} \sum_{i=1}^n X_i X_i K_{a h_n}(\frac{x_i - X_i}{h_n}) g(\beta^T x) x.
\]

Since \( S_n(\beta) \) is of the integration form, to calculate the limiting distribution of \( S_n \), we can first calculate the limiting distribution of the part inside the integral for a fixed \( x \).

Let the parts inside the integral of \( S_n(\beta) \) and \( S(\beta) \) be:

\[
G_n(x; \beta) = \frac{\hat{A}_n(x; \beta) B_n(x; \beta) - A_n(x; \beta) \hat{B}_n(x; \beta) C_n(x),}{\partial \beta^T x},
\]

\[
G(x; \beta) = \frac{\partial A(x; \beta) B(x; \beta) - A(x; \beta) \partial B(x; \beta) C(x,)}{\partial \beta^T x},
\]

where

\[
\hat{A}(x; \beta) = \left\{ m(x, g(\beta^T x)) f_a \left\{ x, g(\beta^T x) \right\} \right\} g(\beta^T x) x,
\]

\[
\hat{B}(x; \beta) = f_a \left\{ x, g(\beta^T x) \right\}.
\]

To prove the limit distribution of \( G_n(\beta) - G(\beta) \), we need the following lemma:

**LEMMA B.1.** If \( (A_n)_{n=1}^\infty \) and \( (B_n)_{n=1}^\infty \) are two sequences of random variables and \( c_n(A_n - A) \to N(0, \Sigma) \) in distribution and \( d_n(B_n - B) \to N(0, \Sigma_B) \) in distribution, where \( c_n/d_n \to 0 \) as \( n \to \infty \). Then:

\[
c_n(A_n B_n - AB) = c_n(A_n - A) B + o_p(1).
\]

**Proof.** Notice that: \( c_n(A_n B_n - AB) = (c_n/d_n) A_n d_n B_n - AB \), where \( d_n(B_n - B) \) converges to a normal distribution, \( A_n \) converges in probability to \( A \) and \( c_n/d_n \to 0 \). Thus the first term is \( o_p(1) \). Then we have \( c_n(A_n B_n - AB) = c_n(A_n - A) B + o_p(1) \).

Under the assumption of the boundedness of the first three derivatives of \( m(x, a) \) and \( f(x, a) \), we can prove that:

\[
E\{ A_n(x; \beta) \} = A(x; \beta) + O(h_n^2 + h_n^2).
\]

Together with the law of large numbers, we obtain that \( A_n(x; \beta) \overset{P}{\to} A(x; \beta) \). Since \( \hat{A}_n(x; \beta) \) is the sum of n i.i.d variables, with the central limit theorem we can obtain that:

\[
\frac{n h_n^2}{2} \left\{ A_n(x; \beta) - A(x; \beta) \right\} \to N(0, h_n^2).
\]

\[
\frac{n h_n^2}{2} \left\{ A_n(x; \beta) - A(x; \beta) \right\} \overset{d}{\to} N(0, h_n^2) + O(h_n^2) + o_p(1).
\]

Thus,

\[
\frac{n h_n^2}{2} \left\{ A_n(x; \beta) - A(x; \beta) \right\} \overset{d}{\to} N(0, h_n^2).
\]

\[
\left\{ A_n(x; \beta) - A(x; \beta) \right\} = \frac{n h_n^2}{2} \left\{ A_n(x; \beta) - A(x; \beta) \right\} \overset{d}{\to} N(0, h_n^2) + O(h_n^2) + o_p(1).
\]

Similarly, we can obtain that, as \( n \to \infty \),

\[
\frac{n h_n^2}{2} \left\{ A_n(x; \beta) - A(x; \beta) \right\} \overset{d}{\to} N(0, h_n^2).
\]

\[
\left\{ A_n(x; \beta) - A(x; \beta) \right\} = \frac{n h_n^2}{2} \left\{ A_n(x; \beta) - A(x; \beta) \right\} \overset{d}{\to} N(0, h_n^2) + O(h_n^2) + o_p(1).
\]

By Lemma B.1 and the above convergence results, we obtain that:

\[
(n h_n^2)^{1/2} \left\{ A_n(x; \beta) - A(x; \beta) \right\} \overset{d}{\to} \frac{1}{\sqrt{n}} \sum_{i=1}^n \Phi_i(x; \beta) + o_p(1),
\]

where

\[
\Phi_i(x; \beta) = \left\{ A_i(x; \beta) - A(x; \beta) \right\} \frac{1}{h_n} K_{a h_n}(\frac{x - X_i}{h_n}) g(\beta^T x) x.
\]

Similar to previous calculations, by the central limit theorem we can prove that \( \frac{1}{\sqrt{n}} \sum_{i=1}^n \Phi_i(x; \beta) \) converges to a normal distribution, where the covariance of the asymptotic distribution is:

\[
\Sigma(\beta) = \frac{1}{h_n} \sum_{i=1}^n \Sigma(\beta) \frac{1}{h_n} K_{a h_n}(\frac{x - X_i}{h_n}) g(\beta^T x) x.
\]

Notice that:

\[
(n h_n^2)^{1/2} \left\{ A_n(x; \beta) - A(x; \beta) \right\} \overset{d}{\to} \frac{1}{\sqrt{n}} \sum_{i=1}^n \Phi_i(x; \beta) + o_p(1).
Together with $C_n(x) \xrightarrow{p} C(x)$, $B_n(x; \beta)$, $B_n(x; \beta)$, $C_n(x)$, we obtain that $B_n(\beta)$ converge in probability to

$$\int \left[ m_{\text{aud}}(x, g(\beta^T x)) \right] (\beta^T x) + m_{\text{aud}}(x, g(\beta^T x)) \| \beta \|^2 {(\beta^T x)} dx = D(\beta).$$

B.3 Proof of Equation (A.4)

For notation, let $X_l$ be the $l$ th component of the vector $x$, and $B_j$ and $B_k$ are the $j$ th and $k$ th component of vector $\beta, j, k, l \in \{1, \ldots, d\}$. Let $S_{n,l}(\beta)$ be the $l$ th component of vector $S_n(\beta)$. Since we have proved that $\hat{\beta}_n - \beta^*$ converge in probability to 0, to prove Equation (A.4) it suffices to show that: $\hat{\beta}^3 S_{n,l}(\beta)/(\partial \beta \partial \beta^T) = O_p(1)$. By calculation, for $j, k, l \in \{1, \ldots, d\}$:

$$\frac{\partial^2}{\partial \beta_j \partial \beta_k} S_{n,l}(\beta)$$

where $\hat{A}_n(x; \beta)$ is the $j$ th component of vector $\hat{A}_n(x; \beta)$ and $B_{n,k}(x; \beta)$ is the $j$ th component of vector $B_{n,k}(x; \beta)$. With similar calculation as before, under the assumption that the first four orders of derivatives of $m(x, a)$ and $f(x, a)$ are bounded, we obtain that:

$$\hat{\beta}^3 S_{n,l}(\beta)/(\partial \beta \partial \beta^T) = O_p(1).$$

C. ESTIMATION OF COVARIANCE

From above, the covariance of the asymptotic distribution for $(n h d^2 h^2)^{1/2} (\hat{\beta}_n - \beta^*)$ is given by $D(\beta) = \Sigma(\beta)D(\beta)$. First, $D(\beta)$ can be estimated with $\hat{D}(\beta)$. Then for the estimation of $\Sigma(\beta)$, notice that:

$$\Sigma(\beta) = \int_{x_1} \int_{x_2} \Sigma_G(x_1, x_2; \beta) dx_1 dx_2 = \int_{x} \Sigma_G(x; \beta) dx,$$

and

$$\Sigma(\beta) = \left( \frac{1}{n} \sum_{i=1}^{n} \left( \Phi_i(x; \beta) \right) C_n(x) \right) B_n(x; \beta) + o_p(1).$$

Therefore, $\Sigma_G(x; \beta) = \Sigma_G(x; \beta) + \Sigma_G(x; \beta)/B_n(x; \beta)$ where $\Sigma_G(x; \beta)$ can be estimated empirically by the sample covariance of $\Phi_i(x; \beta)$. $\Phi_i(x; \beta)$ is approximated by plugging in the $A_n(x; \beta)$, $B_n(x; \beta)$, $C_n(x)$ for $A(x; \beta)$, $B(x; \beta)$ and $C(x)$. Finally, we plug in $\hat{\beta}_n$ for $\beta^*$ to obtain the estimated covariance.