Set-valued dynamic treatment regimes for competing outcomes

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Abstract

Dynamic treatment regimes operationalize the clinical decision process as a sequence of functions, one for each clinical decision, where each function takes as input up-to-date patient information and gives as output a single recommended treatment. Current methods for estimating optimal dynamic treatment regimes, for example Q-learning, require the specification of a single outcome by which the ‘goodness’ of competing dynamic treatment regimes are measured. However, this is an over-simplification of the goal of clinical decision making, which aims to balance several potentially competing outcomes. For example, often a balance must be struck between treatment effectiveness and side-effect burden. We propose a method for constructing dynamic treatment regimes that accommodates competing outcomes by recommending sets of treatments at each decision point. Formally, we construct a sequence of set-valued functions that take as input up-to-date patient information and give as output a recommended subset of the possible treatments. For a given patient history, the recommended set of treatments contains all treatments that are not inferior according to any of the competing outcomes. When there is more than one decision point, constructing these set-valued functions requires solving a non-trivial enumeration problem. We offer an exact enumeration algorithm by recasting the problem as a linear mixed integer program. The proposed methods are illustrated using data from a depression study and from the CATIE schizophrenia study.

1 Introduction

Dynamic treatment regimes (DTRs) attempt to operationalize the clinical decision-making process wherein a clinician selects a treatment based on current patient characteristics and then continues to adjust treatment over time in response to the evolving heath status of the patient. Formally, a DTR is a sequence of decision rules, one for each decision point, that take as input current patient information and give as output a recommended treatment. There is a growing interest in estimating the DTRs from randomized or observational data, typically with the goal of finding the DTR that maximizes the expectation of a chosen clinical outcome. A DTR is said to be optimal if when followed by the population of interest it produces the maximal clinical outcome on average. Optimal DTRs have been estimated for the management of a number of chronic conditions including ADHD [Laber et al., 2011, Nahum-Shani et al., 2010, 2012], depression [Schulte et al., 2012, Song et al., 2012], HIV infection [Moodie et al., 2007], schizophrenia [Shortreed et al., 2011], and cigarette addiction [Strecher et al., 2006]. Approaches for estimating optimal DTRs from data include Q-learning [Nahum-Shani et al., 2010, Watkins, 1989, Watkins and Dayan, 1992], A-learning [Blatt et al., 2004, Murphy, 2003], regret regression [Henderson et al., 2010], and direct value maximization [Orellana et al., 2010, Zhang et al., 2012, Zhao et al., 2012].

When estimating a decision rule from data using any of the aforementioned methods, one must specify a single outcome and neglect all others. Perhaps the most obvious example is seeking the most effective DTR without regard for side-effects. Alternatively, one might attempt to form a linear combination of two outcomes, e.g. side effects and effectiveness, yielding a single composite outcome. However, forming a composite outcome requires the elicitation of a trade-off between two potentially incomparable outcomes. For example, one would need to know that a gain of 1 unit of effectiveness is worth a cost of 3 units of side-effects. Even if one could elicit this trade-off at an aggregate level, assuming that a particular trade-off holds for all future decision-makers is not reasonable since each will have his or her own individual preferences which obviously cannot be known *a priori.* Lizotte et al. [2012] present one approach to dealing with this problem using a method that estimates an optimal DTR for all possible linear trade-offs simultaneously. Their method can also be used to explore what range of trade-offs is consistent with each available treatment. Nonetheless, their method must assume that there exists a *linear* trade-off that adequately describes any outcome preference, and they still (perhaps implicitly) require the elicitation of this trade-off.

We propose an alternative approach for constructing DTRs that is sensitive to competing outcomes but that avoids eliciting trade-offs (linear or otherwise) between outcomes. Instead, our approach only requires we elicit the size of a 'clinically significant' difference on each outcome scale. Our proposed method still allows for the incorporation of clinical judgement, individual patient preferences, cost, and local availability, when no one treatment decision is best across all competing outcomes. Specifically, we propose set-valued DTRs (SVDTRs) which, like DTRs, are a sequence of decision rules, one for each time point. However, the decision rules that comprise a SVDTR take as input current patient information and give as output a *set* of recommended treatments. The recommended treatment set will be a singleton when there exists a treatment that is best across all outcomes and will contain multiple treatments when no single treatment is best.

The contributions of this paper are as follows. We introduce SVDTRs as a new method for operationalizing sequential clinical decision making that allows consideration of competing outcomes and the incorporation of clinical judgment. SVDTRs deal with competing outcomes without having to elicit trade-offs between competing outcomes — they only require the elicitation of what constitutes a clinically significant difference for each outcome individually. We also provide a novel mathematical programming formulation which allows us to efficiently estimate SVDTRs from data.

The remainder of this paper is organized as follows. In Section 2 we review the Q-learning algorithm for estimating optimal DTRs from data. The Q-learning algorithm provides a starting point for the construction of SVDTRs. In Section 3 we propose a SVDTR for the single decision point problem. We then extend this methodology to the two decision point problem in Section 4, and in Section 4.1 we describe our mathematical programming approach for the efficient estimation of SVDTRs from data. In Section 5 we illustrate the construction of SVDTRs using data from a single decision depression trial [Keller et al., 2000] and a two-stage schizophrenia study. For clarity, the main body of the paper considers only binary treatment decisions; we give an extension to an arbitrary number of treatment options in the Appendix.

2 Single outcome decision rules

In this section we review the Q-learning algorithm for estimating an optimal DTR when there is a single outcome of interest. For simplicity, we will consider the case in which there are two decision points and two treatment options at each decision point. In this setting the data available to estimate an optimal DTR are denoted by $\mathcal{D} = \{(H_{1i}, A_{1i}, H_{2i}, A_{2i}, Y_i)\}_{i=1}^{n}$ and consists of n trajectories (H_1, A_1, H_2, A_2, Y), one for each patient, drawn *i.i.d.* from some unknown distribution. We use capital letters like H_1 and A_1 to denote random variables and lower case letters like h_1 and a_1 to denote realized values of these random variables. The components of each trajectory are as follows: $H_t \in \mathbb{R}^{p_t}$ denotes patient information collected prior to the assignment of the tth treatment, thus, this is information the decision maker can use to inform the

tth treatment decision; $A_t \in \{-1, 1\}$ denotes the tth treatment assignment; $Y \in \mathbb{R}$ denotes the outcome of interest which is assumed to be coded so that higher values are more desirable than lower values. The outcome Y is commonly some measure of treatment effectiveness but could also be a composite measure attempting to balance different objectives.

With a single outcome, the goal is to construct a pair of decision rules $\pi = (\pi_1, \pi_2)$ where $\pi_t(h_t)$ denotes a decision rule for assigning treatment at time t to a patient with history h_t in such a way that the expected response Y, given such treatment assignments, is maximized. Formally, if $\mathbb{E}^{\pi}$ denotes the joint expectation over H_t, A_t, and Y under the restriction that $A_t = \pi_t(H_t)$, then the optimal decision rule π^{opt} satisfies $\mathbb{E}^{\pi^{\text{opt}}} Y = \sup_{\pi} \mathbb{E}^{\pi} Y$. Note that the optimal decision rule defined in this way ignores the impact of the DTR π^{opt} on any other outcomes not incorporated into Y.

One method for estimating an optimal DTR is the Q-learning algorithm [Watkins, 1989, Watkins and Dayan, 1992]. Q-learning is an approximate dynamic programming procedure that relies on regression models to approximate the following conditional expectations

$$\begin{aligned} Q_2(h_2, a_2) &\triangleq \mathbb{E}(Y | H_2 = h_2, A_2 = a_2), \\ Q_1(h_1, a_1) &\triangleq \mathbb{E}\left(\max_{a_2 \in \{-1,1\}} Q_2(H_2, a_2) \big| H_1 = h_1, A_1 = a_1 \right). \end{aligned}$$

The function Q_t is termed the stage-t Q-function. The function $Q_2(h_2, a_2)$ measures the quality of assigning treatment a_2 at the second decision point to a patient with history h_2. The function $Q_1(h_1, a_1)$ measures the quality of assigning treatment a_1 at the first decision point to a patient with history h_1 assuming that an optimal treatment decision will be made at the second decision point. From these definitions it is clear that $\pi_2^{\text{opt}}(h_2) = \arg\max_{a_2 \in \{-1,1\}} Q_2(h_2, a_2)$, and, assuming that π_2^{opt} is followed at the second decision point, $\pi_1^{\text{opt}}(h_1) = \arg\max_{a_1 \in \{-1,1\}} Q_1(h_1, a_1)$. Note that this is nothing more than the dynamic programming solution to finding the optimal sequence of decision rules [Bellman, 1957].

In practice, the Q-functions are not known and so a natural approach is to estimate them from data. As is common in practice, we will consider linear working models of the form $Q_t(h_t, a_t) = h_{t,1}^{\intercal} \beta_t + a_t h_{t,2}^{\intercal} \psi_t$, where $h_{t,1}$ and $h_{t,2}$ are (possibly the same) subvectors of h_t. The Q-learning algorithm proceeds in three steps:

1. Estimate the parameters indexing the working model for the stage-2 Q-function using least squares. Let $\hat{\beta}_2$ and $\hat{\psi}_2$ denote the corresponding estimators, and let $\hat{Q}_2(h_2, a_2)$ denote the fitted model.

2. (a) Define the predicted future outcome $\tilde{Y}$ following the estimated optimal decision rule at stage two

as $\tilde{Y} \triangleq \max_{a_2 \in \{-1,1\}} \hat{Q}_2(H_2, a_2)$.

(b) Estimate the parameters indexing the working model for the stage-1 Q-function using least squares. That is, regress $\tilde{Y}$ on H_1 and A_1 using the working model to obtain $\hat{\beta}_1$ and $\hat{\psi}_2$. Let $\hat{Q}_1(h_1, a_2)$ denote the fitted model.

3. Define the Q-learning estimated optimal treatment regime $\hat{\pi} = (\hat{\pi}_1, \hat{\pi}_2)$ so that $\hat{\pi}_t(h_t) = \arg\max_{a_t \in \{-1,1\}} \hat{Q}(h_t, a_t)$.

The Q-learning algorithm is simple to implement and easy to interpret given its connections to dynamic programming. For these reasons we use Q-learning as the basis for developing SVDTRs which we introduce in the next section. However, Q-learning is not the only procedure for estimating an optimal DTR. Alternatives to Q-learning include A-learning [Blatt et al., 2004, Murphy, 2003, Schulte et al., 2012], regret regression [Henderson et al., 2010], and penalized Q-learning [Song et al., 2012].

Penalized Q-learning also lends itself to producing SVDTRs, though of a different nature. Briefly, penalized Q-learning employs an unusual singular penalty to estimate the coefficients in the second stage Q-function. For a given tuning parameter $\lambda > 0$ estimated coefficients $\tilde{\beta}_2$ and $\tilde{\psi}_2$ satisfy

$$(\tilde{\beta}_2^\intercal, \tilde{\psi}_2^\intercal)^\intercal = \arg \min_{\beta_2, \psi_2 \in \mathbb{R}^{p_2}} \sum_{i=1}^{n} (Y_i - H_{2,1,i}^\intercal \beta_2 - A_{2i} H_{2,2,i}^\intercal \psi_2)^2 + \lambda \sum_{i=1}^{n} |H_{2,2,i}^\intercal \psi_2|.$$

Using this approach, under certain generative models, $H_{2,2}^\intercal \tilde{\psi}_2$ will be exactly zero for a non-null set of H_2 values [see Song et al., 2012, for details]. One can then define the set-valued second stage decision rule

$$\tilde{\pi}(h_2) = \begin{cases} \{\mathrm{sgn}(h_{2,2}^\intercal \tilde{\psi}_2)\}, \text{ if } h_{2,2}^\intercal \tilde{\psi}_2 \neq 0, \\ \{-1, 1\}, \text{ otherwise.} \end{cases}$$

The foregoing set-valued decision rule assigns a single treatment for second stage histories h_2 that, based on the estimated coefficient $\tilde{\psi}_2$ have a nonzero treatment effect. On the other hand, if the estimated treatment effect $h_{2,2}^\intercal \tilde{\psi}_2$ is zero, then both treatments are recommended. An analogous approach could be used to form a set-valued decision rule at the first stage.

In the preceding development we have adapted the ideas of Song et al. [2012] to suit our purposes. They proposed penalized Q-learning in an effort to improve coverage probabilities of confidence intervals for first stage coefficients. Thus, any problems with this development are ours and should not be attributed to Song et al. [2012]. Secondly, such set-valued treatment regimes attempt to recommend sets of treatment when there is insufficient evidence of a significant treatment effect with respect to a single outcome measure for a patient with a given history. This should be contrasted with our goal of balancing the treatment effects of competing outcomes.

3 Static set-valued decision rules

In this section we discuss the estimation of a set-valued decision rule when there is a single decision point and there are two competing outcomes of interest (see the Appendix for the generalization to an arbitrary number of treatment options). The data available to estimate the decision rule is denoted by $\mathcal{D} = \{(H_i, A_i, Y_i, Z_i)\}_{i=1}^{n}$ and is comprised of n trajectories (H, A, Y, Z) drawn independently from the same distribution. The elements of each trajectory are as follows: H denotes the information available to the decision maker *before* the assignment of treatment and is assumed to take values in $\mathbb{R}^p$; A denotes the randomly assigned treatment which is assumed to be binary and coded to take values in the set $\{-1, 1\}$; Y denotes the first outcome of interest which is assumed to take values in $\mathbb{R}$ and is coded so that higher values of Y correspond to more desirable clinical outcomes; and Z denotes the second outcome of interest which is assumed to take values in $\mathbb{R}$ and is also coded so that higher values are more desirable. It is also assumed that one has obtained, either by elicitation or historical data, the positive quantities Δ_Y and Δ_Z denoting 'clinically meaningful differences' in the outcomes Y and Z respectively. That is, a clinician would be willing to change a patient's current treatment if this change yielded a difference of at least Δ_Y (Δ_Z) in the outcome Y (Z) and all other things were held equal. Note that in eliciting Δ_Y there is no need to reference the competing outcome Z and vice versa when eliciting Δ_Z.

The goal is to construct a decision rule $\pi : \mathbb{R}^p \to \{\{-1\}, \{1\}, \{-1, 1\}\}$ that maps baseline patient information H into a subset of the available treatment decisions. Ideally, for a given baseline history h, the decision rule π would recommend a single treatment if that treatment was expected to yield a clinically meaningful improvement in at least one of the outcomes and, in addition, that treatment was not expected to lead to a significant detriment in terms of the other outcome. On the other hand, if this cannot be said of one the treatments then the decision rule should instead return the set $\{-1, 1\}$ and leave the 'tie-breaking' to the decision maker. Put more formally, if we define the (non-normalized) treatment effects for each outcome as $r_Y(h) \triangleq \mathbb{E}(Y|H = h, A = 1) - \mathbb{E}(Y|H = h, A = -1)$ and similarly $r_Z(h) \triangleq \mathbb{E}(Y|H = h, A = 1) - \mathbb{E}(Y|H =$

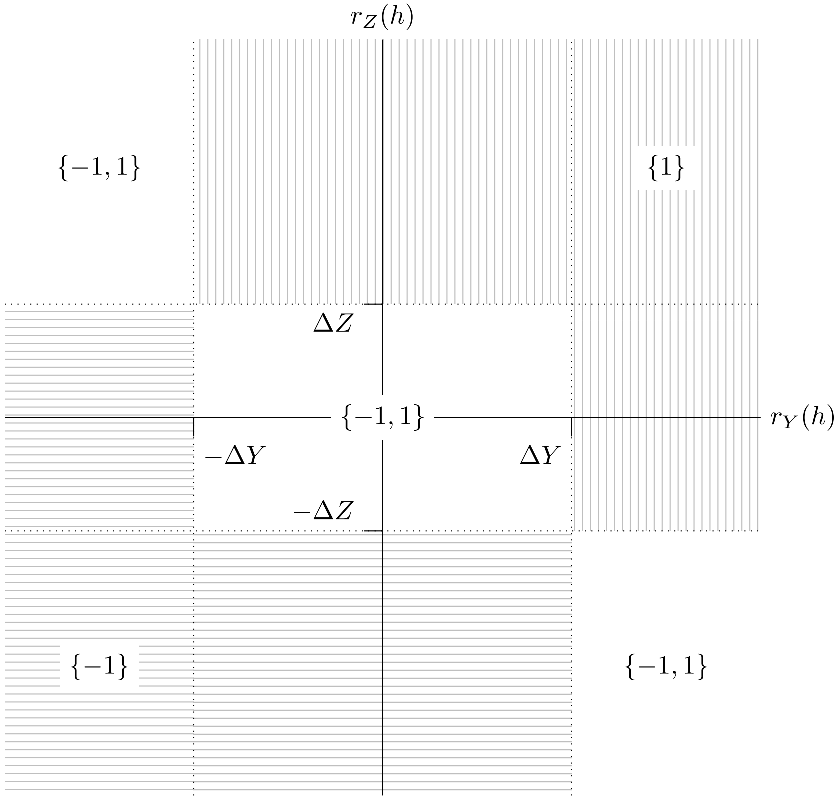

Figure 1: Diagram showing how the output of $\pi^{\text{Ideal}}(h)$ depends on Δ_Y and Δ_Z, and on the location of the point $(r_Y(h), r_Z(h))$.

$h, A=-1)$, then the ideal decision rule satisfies

$$\pi_{\Delta}^{\text{Ideal}}(h) = \begin{cases} \{\text{sgn}(r_Y(h))\}, \text{ if } |r_Y(h)| \geq \Delta_Y \text{ and } \text{sgn}(r_Y(h))r_Z(h) > -\Delta_Z, \\ \{\text{sgn}(r_Z(h))\}, \text{ if } |r_Z(h)| \geq \Delta_Z \text{ and } \text{sgn}(r_Z(h))r_Y(h) > -\Delta_Y, \\ \{-1,1\}, \text{ otherwise,} \end{cases} \tag{1}$$

where sgn denotes the signum function. Figure 1 illustrates how $\pi_{\Delta}^{\text{Ideal}}(h)$ depends on $r_Y(h)$, $r_Z(h)$, Δ_Y, and Δ_Z. If we consider the point $(r_Y(h), r_Z(h)) \in \mathbb{R}^2$, its location relative to the points (Δ_Y, Δ_Z), $(-\Delta_Y, \Delta_Z)$, $(\Delta_Y, -\Delta_Z)$ and $(-\Delta_Y, -\Delta_Z)$ determines whether we prefer treatment 1, prefer treatment -1, or are indifferent according to the criteria set out above.

Following the motivation for Q-learning, we will estimate the ideal decision by modelling the conditional expectations $Q_Y(h,a) \triangleq \mathbb{E}(Y|H=h, A=a)$ and $Q_Z(h,a) \triangleq \mathbb{E}(Z|H=h, A=a)$. We will use linear working models of the form

$$
\begin{aligned}
Q_Y(h,a) &= h_{1,1,Y}^{\intercal}\beta_Y + a h_{1,2,Y}^{\intercal}\psi_Y, && (2)\\
Q_Z(h,a) &= h_{1,1,Z}^{\intercal}\beta_Z + a h_{1,2,Z}^{\intercal}\psi_Z, && (3)
\end{aligned}
$$

where $h_{1,1,Y}$, $h_{1,2,Y}$, $h_{1,1,Z}$, and $h_{1,2,Z}$ are (possibly the same) subvectors of h, and estimate the coefficients β_Y, ψ_Y, β_Z, and ψ_Z using least squares. In the remainder of this Section, in an effort to avoid cumbersome notation, we will assume $h_{i,j,Z}$ and $h_{i,j,Y}$ are equal and thus can be denoted as $h_{i,j}$. This assumption is only for notational efficiency and is not used in Section 5. Let $\hat{\beta}_Y, \hat{\psi}_Y, \hat{\beta}_Z$, and $\hat{\psi}_Z$ denote the corresponding least squares estimators. Note that the implied estimators of $r_Y(h)$ and $r_Z(h)$ are $2h_{2,1}^{\intercal}\hat{\psi}_Y$ and $2h_{2,1}^{\intercal}\hat{\psi}_Z$ respectively. Hence, a simple plug-in estimator of the ideal decision rule is given by

$$
\hat{\pi}_{\Delta}(h) = \begin{cases} \{\mathrm{sgn}(h_{1,2}^{\intercal}\hat{\psi}_Y)\}, \text{ if } 2|h_{1,2}^{\intercal}\hat{\psi}_Y| \geq \Delta_Y \text{ and } \mathrm{sgn}(h_{1,2}^{\intercal}\hat{\psi}_Y)2h_{1,2}^{\intercal}\hat{\psi}_Z > -\Delta_Z, \\ \{\mathrm{sgn}(h_{1,2}^{\intercal}\hat{\psi}_Z)\}, \text{ if } 2|h_{1,2}^{\intercal}\hat{\psi}_Z| \geq \Delta_Z \text{ and } \mathrm{sgn}(h_{1,2}^{\intercal}\hat{\psi}_Z)2h_{1,2}^{\intercal}\hat{\psi}_Y > -\Delta_Y, \\ \{-1,1\}, \text{ otherwise.} \end{cases} \qquad (4)
$$

The above decision rule mimics the ideal decision rule and is easily shown to be consistent under mild moment conditions and the assumption that the working models in (2) and (3) are correct. While the above model is a compact representation of $\hat{\pi}_{\Delta}$, it will often be convenient to display the decision rule either as a tree or as regions in the $h_{1,2}^{\intercal}\hat{\psi}_Y$, $h_{1,2}^{\intercal}\hat{\psi}_Z$ plane (see Section 5 for examples).

3.1 Preference heterogeneity and set-valued rules

Personalized medicine recognizes the need to account for heterogeneity in treatment effects across patients. However, it is important to recognize not only that different patients will experience different outcomes under the same treatments, but also that different patients will rate *the same outcomes* differently. In this section we illustrate how set-valued decision rules can accommodate patient individual preference even though such preferences cannot be known at the time the data are collected and the models are estimated. We contrast set-valued decision rules with single outcome decision rules formed using a composite outcome. We shall see that when the composite outcome closely reflects patient preferences then the corresponding decision rule performs well, however, when the composite outcome does not reflect patient preferences, then the quality of the single outcome decision rule can perform poorly.

We will consider data generated from the following simple class of generative models

$$\begin{aligned}
&H = (H_1, H_2)^\intercal \sim \text{Normal}_2\left(0, \Omega\right),\\
&A \sim \text{Uniform}\{-1, 1\},\\
&Y = A(\psi_{Y,1} + \psi_{Y,2}H_1 + \psi_{Y,3}H_2 + \psi_{Y,4}H_1H_2),\\
&Z = A(\psi_{Z,1} + \psi_{Z,2}H_1 + \psi_{Z,3}H_2 + \psi_{Z,4}H_1H_2),
\end{aligned}$$

where $\Omega_{1,1} = \Omega_{2,2} = 1$, and $\Omega_{1,2} = \Omega_{1,2} = \rho$. Thus, the class of models is determined by ψ_Y, ψ_Z, ρ, and the thresholds Δ_Y and Δ_Z. Note that we have omitted specifying a main-effect term in the conditional mean of the outcomes Y and Z since these do not affect the optimal decision rule; similarly, we have assumed that Y and Z are observed without error since an independent additive error would not affect the optimal decision rule. We vary the parameters indexing the generative models in order to highlight factors that affect the performance of the set-valued decision rule. In particular, we systematically vary the following three components of the generative model: (i) the proportion of individuals for which there is a unique best treatment option (Uniq); (ii) the proportion of individuals for which neither treatment yields a significant treatment effect on either outcome (Null); and (iii) the proportion of individuals for which there are significant treatment effects for both outcomes but the effects run in opposite directions (Opst). More specifically, define

$$\begin{aligned}
\texttt{Uniq} &\triangleq P\Big(\big\{|r_Y(H)| \geq \Delta_Y, \text{sgn}(r_Y(H))r_Z(H) \geq -\Delta_Z\big\} \bigcup \\
&\qquad\qquad \big\{|r_Z(H)| \geq \Delta_Z, \text{sgn}(r_Z(H))r_Y(H) \geq -\Delta_Y)\big\}\Big);\\
\texttt{Null} &\triangleq P\left(\{|r_Y(H)| < \Delta_Y\} \bigcap \{|r_Z(H)| < \Delta_Z\}\right); \text{ and}\\
\texttt{Opst} &\triangleq P\left(|r_Y(H)| \geq \Delta_Y,\ |r_Z(H)| \geq \Delta_Z,\ r_Y(H)r_Z(H) < 0\right).
\end{aligned}$$

Note that Uniq, Null, Opst sum to one. The three settings for Uniq, Null, and Opst that we consider here and the corresponding values of $\psi_Y, \psi_Z, \rho, \Delta_Y$, and Δ_Z are given in Table 3.1.

Setting	Uniq	Null	Opst	ψ_Y	ψ_Z	ρ	Δ_Y	Δ_Z
1	0.80	0.10	0.10	$(-0.30, 0.25, -2.0)$	$(0.0, -0.72, -0.74)$	-0.38	0.5	0.5
2	0.45	0.10	0.45	$(-0.05, 0.40, -1.25)$	$(0.65, -0.85, 0.29)$	$-.36$	0.5	0.5
3	0.10	0.10	0.80	$(-1.0, -1.4, 2.0)$	$(1.6, 2.2, -2.2)$	-0.4	0.5	1.0

Table 1: Settings for parameters indexing the underlying generative model. The settings vary from mostly individuals with unique best treatments to mostly individuals with significant treatment effects running in opposite directions.

In this example, patient preference is operationalized through what we term the preference parameter $\delta \in [0,1]$, similar to the approach of Lizotte et al. [2012]. A preference of δ indicates that a patient would be ambivalent between a one unit improvement (detriment) in Z and a $\delta/(1-\delta)$ improvement (detriment) in Y. For patients with preference parameter δ the optimal decision rule is given by $\pi_{c,\delta}(h) \triangleq \arg\max_a \mathbb{E}(\delta Y + (1-\delta)Z|H = h, A = a)$; thus, the optimal composite outcome is given by $\delta Y + (1-\delta)Z$. Below we will compare decision rules derived from the set-valued decision rule of the preceding section with $\pi_{c,0.5}$ and $\pi_{c,0.25}$.

For a patient's 'true preference' δ^* define the *regret* of an arbitrary decision rule π as

$$\mathbb{E}\left[\mathbb{E}(\delta^* Y + (1-\delta^*)Z|H, A = \pi(H)) - \max_a \mathbb{E}(\delta^* Y + (1-\delta^*)Z|H, A = a)\right],$$

so that the regret measures the average loss in performance incurred by applying a suboptimal decision rule π. The regret is nonnegative and equals zero when π agrees with the optimal decision rule, π_{c,δ^*}, almost surely.

In order to define the regret for a set-valued decision rule one must specify a mechanism for choosing a treatment from the set of recommended treatments. Here we consider two possible 'tie-breaking' scenarios. In the first, we assume that the clinician will choose the best action from among the recommended treatments with probability 0.75; we believe this reflects a clinicians ability to leverage individual patient characteristics and preferences in the decision process. Recall that the set-valued decision rule provides not only the pool of recommended treatments but also the estimated mean outcomes for each response; thus this information can be used to inform the clinician's decision. We term the resultant (random) decision rule the 75% optimal compatible policy. In the second tie-breaking scenario we imagine an adversarial decision maker that always chooses the worst of the available treatments. Such a decision maker was considered by Milani Fard and Pineau [2011] in the study of non-deterministic decision rules for a single outcome. While a clinician that is actively working against their patients is unrealistic, the performance of such a policy is useful for illustrating the impact of screening out suboptimal treatments which occurs in the formation of the set-valued decision rule. We term the resultant (deterministic) decision rule the 0% optimal compatible policy. To provide additional baselines for comparison with the 75% and 0% optimal compatible polices, we also consider a policy in which a clinician chooses the optimal treatment from among *all* possible treatments 75% of the time and a policy in which the clinician always chooses the worst possible treatment from among *all* possible treatments; we term these policies the 75% optimal policy and 0% optimal policy respectively.

Figure 3.1 compares the regret of composite-outcome based policies $\pi_{c,0.5}$ and $\pi_{c,0.25}$ with set-valued-

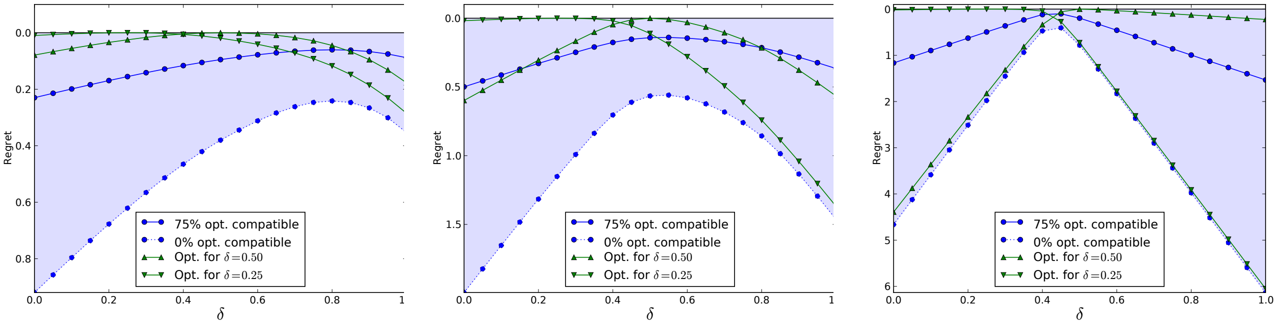

Figure 2: Regret versus patient preference for the 75% and 0% consistent policies as well as $\pi_{c,0.5}$ and $\pi_{c,0.25}$. The blue shaded region indicates the space of all policies that are compatible with the set-valued decision rule. From left to right: parameter settings 1, 2, and 3.

policy-derived 75% and 0% optimal compatible policies across a range of patient preferences. When there is a small fraction of individuals with significant treatment effects running in opposite directions (e.g., setting 1, when `Opst` is small) then the composite outcome based policies perform well unless the preference is grossly misspecified. However, when there is a moderate to large fraction of individuals with significant treatment effects running in opposing directions (e.g., settings 2 and 3, when `Opst` is moderate and large) then using a composite outcome based on only a slightly misspecified patient preference can lead to regrets near the 0% optimal compatible policy! In contrast, the 75% optimal compatible policy remains relatively stable across all three settings and all patient preferences even though no patient preference information is required to estimate the set-valued decision rule. Figure 3.1 compares the regret of the 75% and 0% optimal policies with the 75% and 0% optimal compatible policies. When there are many individuals with unique best treatments (e.g., setting 1, when `Uniq` is large) then the set-valued decision rule screens many suboptimal treatments and we see that the 75% optimal policy is dominated by the 0% optimal compatible policy. As there are fewer individuals with unique optimal treatments the difference between the 75% optimal compatible and 75% optimal policies as well as the difference between the 0% optimal compatible and 0% optimal policies converges to zero. The reason for this is clear, as there are a smaller number of unique best treatments fewer suboptimal treatments are screened out.

4 Dynamic set-valued decision rules

In this section we extend set-valued decision rules to the case with two decision points and two competing outcomes. In order to make this extension we will need to generalize the notation from the previ-

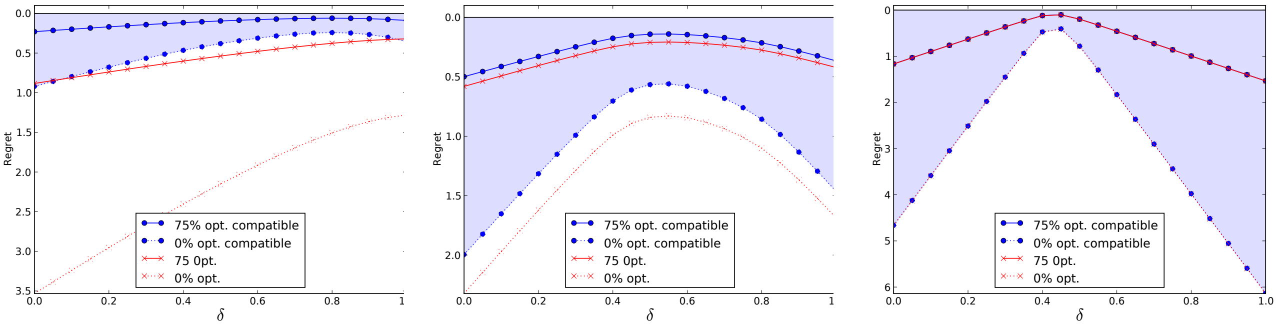

Figure 3: Regret versus patient preference for the 75% and 0% consistent policies as well as $\pi_{c,0.5}$ and $\pi_{c,0.25}$. The blue shaded region indicates the space of all policies that are compatible with the set-valued decision rule. From left to right: parameter settings 1, 2, and 3.

ous section. The data available estimate a pair of decision rules, one for each time point, is denoted by $\mathcal{D} = \{(H_{1,i}, A_{1,i}, H_{2,i}, A_{2,i}, Y_i, Z_i)\}_{i=1}^{n}$ and is comprised of trajectories (H_1, A_1, H_2, A_2, Y) drawn independently from a fixed but unknown distribution. The elements in each trajectory are as follows: $H_t \in \mathbb{R}^{p_t}$, $t = 1, 2$ denotes the patient information available to the decision maker *before* the tth decision point[1]; $A_t \in \{-1, 1\}$, for $t = 1, 2$ denotes the randomly assigned treatment at the tth stage; $Z, Y \in \mathbb{R}$ denotes competing outcomes observed sometime after the assignment of the second treatment A_2. As in the previous section, we assume that both Y and Z are coded so that higher values are preferred. Also available are the quantities Δ_Y and Δ_Z denoting clinically relevant quantities for Y and Z respectively.

The goal is to construct a pair of decision rules $\pi = (\pi_1, \pi_2)$ where $\pi_t : \mathbb{R}^{p_t} \to \{\{-1, 1\}, \{-1\}, \{1\}\}$ maps up-to-date patient information to a subset of the possible decisions. Like the ideal static decision rule considered in the previous section, for a patient with second stage history h_2, the ideal second stage decision rule, $\pi_{2\Delta}^{\text{Ideal}}$, should recommend a single treatment if that treatment is expected to yield a clinically meaningful improvement in one or both of the outcomes without leading to significant loss in either. Thus, by straightforward extension of the notation for the static-decision case we have,

$$\pi_{2\Delta}^{\text{Ideal}}(h_2) = \begin{cases} \{\text{sgn}(r_{2Y}(h_2))\}, \text{ if } |r_{2Y}(h_2)| \geq \Delta_Y \text{ and } \text{sgn}(r_{2Y}(h_2)) r_{2Z}(h_2) > -\Delta_Z, \\ \{\text{sgn}(r_{2Z}(h_2))\}, \text{ if } |r_{2Z}(h_2)| \geq \Delta_Z \text{ and } \text{sgn}(r_{2Z}(h_2)) r_{2Y}(h_2) > -\Delta_Y, \\ \{-1, 1\}, \text{ otherwise}, \end{cases} \tag{5}$$

where $r_{2Y}(h_2) \triangleq \mathbb{E}(Y|H_2 = h_2, A_2 = 1) - \mathbb{E}(Y|H_2 = h_2, A_2 = -1)$ and similarly, $r_{2Z}(h_2) \triangleq \mathbb{E}(Z|H_2 = h_2, A_2 = 1) - \mathbb{E}(Z|H_2 = h_2, A_2 = -1)$.

[1] Note that H_2 may contain some or all of the vector $(A_1, H_1^{\intercal})^{\intercal}$.

We now define $\pi_{1\Delta}^{\text{Ideal}}$ given that a clinician always selects treatments from the set-valued decision rule $\pi_{2\Delta}^{\text{Ideal}}$ at the second stage. This problem is complicated by the fact that, unlike in the standard setting, there exists a set of histories h_2 at the second stage—those for which $\pi_{2\Delta}^{\text{Ideal}}(h_2) = \{-1, 1\}$—where we do not know the treatment that would be chosen. To address this, we begin by assuming we know that some particular *non*-set-valued decision rule τ_2 will be used at the second stage; we will then consider an appropriate set of possible τ_2 in order to define $\pi_{1\Delta}^{\text{Ideal}}$.

Suppose that a clinician uses the non-set-valued decision rule $\tau_2 : \mathbb{R}^{p_2} \to \{-1, 1\}$ to assign treatments to patients at the second decision point. That is, if a patient presents with history h_2 then the clinician will assign treatment $\tau_2(h_2)$. What is the ideal decision rule at the first decision point knowing that the clinician is using τ_2 to assign treatments at the second decision point? For any function $\tau_2 : \mathbb{R}^{p_2} \to \{-1, 1\}$ define $Q_{2Y}(h_2, \tau_2) \triangleq \mathbb{E}(Y | H_2 = h_2, A_2 = \tau_2(h_2))$. Furthermore, define $Q_{1Y}(h_1, a_1, \tau_2) \triangleq \mathbb{E}(Q_{2Y}(H_2, \tau_2) | H_1 = h_1, A_1 = 1)$ so that $Q_{1Y}(h_1, a_1, \tau_2)$ is the expected outcome for a patient with first stage history $H_1 = h_1$ treated at the first decision point with $A_1 = a_1$ and the decision rule τ_2 at the second decision point. Replacing Y with Z above gives the definitions of $Q_{2Z}(h_2, \tau_2)$ and $Q_{1Z}(h_1, a_1, \tau_2)$. Thus, if it is known that a clinician will follow τ_2 at the second decision point, then the ideal decision rule at the first decision point is given by

$$\pi_{1\Delta}^{\text{Ideal}}(h_1, \tau_2) = \begin{cases} \{\text{sgn}(r_{1Y}(h_1, \tau_2))\}, \text{ if } |r_{1Y}(h_1, \tau_2)| \geq \Delta_Y \text{ and } \text{sgn}(r_{1Y}(h_1, \tau_2)) r_{1Z}(h_1, \tau_2) > -\Delta_Z, \\ \{\text{sgn}(r_{1Z}(h_1, \tau_2))\}, \text{ if } |r_{1Z}(h_1, \tau_2)| \geq \Delta_Z \text{ and } \text{sgn}(r_{1Z}(h_1, \tau_2)) r_{1Y}(h_1, \tau_2) > -\Delta_Y, \\ \{-1, 1\}, \text{ otherwise,} \end{cases} \tag{6}$$

where $r_{1Y}(h_1, \tau_2) \triangleq Q_{1Y}(h_1, 1, \tau_2) - Q_{1Y}(h_1, -1, \tau_2)$, and similarly $r_{1Z}(h_1, \tau_2) \triangleq Q_{1Z}(h_1, 1, \tau_2) - Q_{1Z}(h_1, -1, \tau_2)$. Note that $\pi_{1\Delta}^{\text{Ideal}}(h_2, \tau_2)$ assigns a single treatment if that treatment is expected to yield a clinically meaningful improvement on one or both the outcomes while not causing clinically meaningful loss in either outcome whilst *accounting for the clinician's behavior at the second decision point*, assuming that behaviour is described by the non-set-valued rule τ_2.

We now describe how to construct the ideal decision rule at the first decision point when the rule at the second decision point is set-valued. We say a *non*-set-valued rule τ_2 is *compatible* with a set-valued decision rule π_2 if and only if

$$\tau_2(h_2) \in \pi_2(h_2) \quad \forall h_2 \in \mathbb{R}^{p_2}. \tag{7}$$

Let $\mathcal{C}(\pi_{2\Delta}^{\text{Ideal}})$ be the set of all rules that are compatible with $\pi_{2\Delta}^{\text{Ideal}}$. We define $\pi_{1\Delta}^{\text{Ideal}}$ to be a set-valued decision rule

$$\pi_{1\Delta}^{\text{Ideal}}(h_1) = \bigcup_{\tau \in \mathcal{C}(\pi_{2\Delta}^{\text{Ideal}})} \pi_{1\Delta}^{\text{Ideal}}(h_1, \tau). \tag{8}$$

Our motivation for this definition is driven by a desire to maintain as much choice as possible at stage 1, while making as few assumptions about future behaviour as possible. We assume only that in the future some τ_2 in accordance with π_2 will be followed. Therefore at stage 1 we only eliminate actions for which there exists *no compatible future decision rule* that makes that action a desirable choice.

Note that if we do not assume a particular functional form for τ, the set $\mathcal{C}(\pi_{2\Delta}^{\text{Ideal}})$ will be very large, and computing the union (8) will be intractable. In practice, we will see that the modelling choices made in order to estimate Q_{2Y} and Q_{2Z} suggest a reasonable subset of $\mathcal{C}(\pi_{2\Delta}^{\text{Ideal}})$ over which we will take the union (8) instead. We will provide a mathematical programming formulation that allows us to use existing optimization algorithms to efficiently compute the union over this smaller subset.

We now turn to the estimation of $\pi_{1\Delta}^{\text{Ideal}}$ and $\pi_{2\Delta}^{\text{Ideal}}$ from data. First, we note that to estimate the ideal second decision rule we simply apply the results for the static set-valued decision rule developed in the previous section. That is, we postulate linear models for second stage Q-functions, say, of the form

$$\begin{aligned} Q_{2Y}(h_2, a_2) &= h_{2,1}^{\intercal}\beta_{2Y} + a_2 h_{2,2}^{\intercal}\psi_{2Y}, \\ Q_{2Z}(h_2, a_2) &= h_{2,1}^{\intercal}\beta_{2Z} + a_2 h_{2,2}^{\intercal}\psi_{2Z}, \end{aligned}$$

which we estimate using least squares. The estimated ideal second stage set-valued decision rule $\hat{\pi}_{2\Delta}$ takes the form given in (4). In order to estimate the ideal decision rule at the first decision point we must characterize how a clinician might assign treatments at the second decision point. We make the assumption that clinicians' behavior, denoted τ_2, is *compatible* with $\hat{\pi}_{2\Delta}$ as defined in (20), and we assume that τ_2 can be expressed as a thresholded linear function of h_2. We call such decision rules *feasible* for $\hat{\pi}_{2\Delta}$, and we define the set of feasible decision rules at stage 2 by

$$\mathcal{F}(\hat{\pi}_{2\Delta}) \triangleq \left\{\tau_2 : \exists \rho \in \mathbb{R}^{p_2} \text{ s.t. } \tau_2(h_2) = \text{sgn}(h_{2,2}^{\intercal}\rho) \text{ and } \tau_2 \in \mathcal{C}(\hat{\pi}_{2\Delta})\right\}.$$

Thus, $\mathcal{F}(\hat{\pi}_{2\Delta})$ denotes the collection of second stage non-set-valued decision rules that a clinician might follow if they were presented with $\hat{\pi}_{2\Delta}$. Note that $\mathcal{F}(\hat{\pi}_{2\Delta})$ is non-empty since $\text{sgn}(h_{2,2}^{\intercal}(\frac{1}{2\Delta_Y}\hat{\psi}_{2Y} + \frac{1}{2\Delta_Z}\hat{\psi}_{2Z}))$

belongs to $\mathcal{F}(\hat{\pi}_{2\Delta})$. For an arbitrary $\tau_2 \in \mathcal{F}(\hat{\pi}_{2\Delta})$ define the working models

$$\begin{aligned} Q_{1Y}(h_1, a_1, \tau_2) &= h_{1,1}^{\intercal}\beta_{1Y}(\tau_2) + a_1 h_{1,2}^{\intercal}\psi_{1Y}(\tau_2), \\ Q_{1Z}(h_1, a_1, \tau_2) &= h_{1,1}^{\intercal}\beta_{1Z}(\tau_2) + a_1 h_{1,2}^{\intercal}\psi_{1Z}(\tau_2), \end{aligned} \tag{9}$$

where $\beta_{1Y}(\tau_2), \psi_{1Y}(\tau_2), \beta_{1Z}(\tau_2)$, and $\psi_{1Z}(\tau_2)$ are coefficient vectors specific to τ_2. For a fixed τ_2 one can estimate these coefficients by regressing $\hat{Q}_{2Y}(H_2, \tau_2) = H_{2,1}^{\intercal}\hat{\beta}_{2Y} + \tau_2(H_2)H_{2,2}^{\intercal}\hat{\psi}_2$ and $\hat{Q}_{2Z}(H_2, \tau_2) = H_{2,1}^{\intercal}\hat{\beta}_{2Z} + \tau_2(H_2)H_{2,2}^{\intercal}\hat{\psi}_{2Z}$ on H_1 and A_1 using the working models in (9). Let $\hat{Q}_{1Y}(h_1, a_1, \tau_2)$ and $\hat{Q}_{1Z}(h_1, a_1, \tau_2)$ denote these fitted models, and let $\hat{r}_{1Y} \triangleq \hat{Q}_{1Y}(h_1, 1, \tau_2) - \hat{Q}_{1Y}(h_1, -1, \tau_2)$, and $\hat{r}_{1Z} \triangleq \hat{Q}_{1Z}(h_1, 1, \tau_2) - \hat{Q}_{1Z}(h_1, -1, \tau_2)$. We then define

$$\hat{\pi}_{1\Delta}^{\text{Ideal}}(h_1, \tau_2) = \begin{cases} \{\text{sgn}(\hat{r}_{1Y}(h_1, \tau_2))\}, \text{ if } |\hat{r}_{1Y}(h_1, \tau_2)| \geq \Delta_Y \text{ and } \text{sgn}(\hat{r}_{1Y}(h_1, \tau_2))\hat{r}_{1Z}(h_1, \tau_2) > -\Delta_Z, \\ \{\text{sgn}(\hat{r}_{1Z}(h_1, \tau_2))\}, \text{ if } |\hat{r}_{1Z}(h_1, \tau_2)| \geq \Delta_Z \text{ and } \text{sgn}(\hat{r}_{1Z}(h_1, \tau_2))\hat{r}_{1Y}(h_1, \tau_2) > -\Delta_Y, \\ \{-1, 1\}, \text{ otherwise}, \end{cases} \tag{10}$$

and we define

$$\hat{\pi}_{1\Delta}(h_1) = \bigcup_{\tau_2 \in \mathcal{F}(\hat{\pi}_{2\Delta})} \hat{\pi}_{1\Delta}(h_1, \tau_2). \tag{11}$$

Thus, $\hat{\pi}_{1\Delta}$ is a set-valued decision rule that assigns a single treatment if only that treatment leads to an (estimated) expected clinically meaningful improvement on one or both outcomes and does not lead to a clinically meaningful loss in either outcome across all the treatment rules in $\mathcal{F}(\hat{\pi}_{2\Delta})$ that a clinician might consider at the second stage. Alternatives to this definition of $\hat{\pi}_{1\Delta}$ are discussed in Section 6.

4.1 Computation

Computing $\hat{\pi}_{1\Delta}(h_1)$ requires solving what appears to be a difficult enumeration problem. Nevertheless, exact computation of $\hat{\pi}_{1\Delta}(h_1)$ is possible and (11) can be solved quickly when p_2 is small.

First, note that if τ_2 and τ_2' are decision rules at the second stage that agree on the observed data $\mathcal{D}$, that is, $\tau_2(h_{2i}) = \tau_2'(h_{2i})$ for all values h_{2i} in $\mathcal{D}$, then $\hat{\psi}_{1Y}(\tau_2) = \hat{\psi}_{1Y}(\tau_2')$ and $\hat{\psi}_{1Z}(\tau_2) = \hat{\psi}_{1Z}(\tau_2')$. It follows that $\hat{\pi}_{1\Delta}(h_1, \tau_2) = \hat{\pi}_{1\Delta}(h_1, \tau_2')$ $\forall h_1 \in H_1$. Thus, if we consider a finite subset $\tilde{\mathcal{F}}(\hat{\pi}_{2\Delta})$ of $\mathcal{F}(\hat{\pi}_{2\Delta})$ that contains one decision rule for each possible "labeling" of the stage 2 histories contained in $\mathcal{D}$, then we have

$$\hat{\pi}_{1\Delta}(h_1) = \bigcup_{\tau_2 \in \mathcal{F}(\hat{\pi}_{2\Delta})} \hat{\pi}_{1\Delta}(h_1, \tau_2) = \bigcup_{\tau_2 \in \tilde{\mathcal{F}}(\hat{\pi}_{2\Delta})} \hat{\pi}_{1\Delta}(h_1, \tau_2). \tag{12}$$

We use the term "labeling" by analogy with classification: histories at stage 2 are given a binary "label" by τ_2 which is either 1 or -1. Rather than taking a union over the potentially uncountable $\mathcal{F}(\hat{\pi}_{2\Delta})$, we will enumerate the finite set of all feasible *labelings* of the observed data, place a corresponding τ_2 for each one into the set $\tilde{\mathcal{F}}(\hat{\pi}_{2\Delta})$, and take the union over $\tilde{\mathcal{F}}(\hat{\pi}_{2\Delta})$ instead.

We say that a labeling $\ell_i, i = 1, \ldots, n$ is *compatible* with a set-valued decision rule $\hat{\pi}_{2\Delta}$ if $\ell_i \in \hat{\pi}_{2\Delta}(h_{2,i}), i = 1, \ldots, n$ and *feasible* if it can be induced by a feasible decision rule $\tau_2 \in \mathcal{F}(\hat{\pi}_{2\Delta})$. Equivalently, the labeling is feasible if it is both compatible with $\hat{\pi}_{2\Delta}$ and if the two sets $\{h_{2i} | \ell_i = 1\}$ and $\{h_{2i} | \ell_i = -1\}$ are *linearly separable* in $\mathbb{R}^{p_2}$. Our algorithm for computing $\tilde{\mathcal{F}}(\hat{\pi}_{2\Delta})$ works by specifying a mixed integer linear program with indicator constraints[2] whose feasible solutions correspond to the linearly separable labelings of $\mathcal{D}$ that are compatible with $\hat{\pi}_{2\Delta}$.

First, we note that determining whether or not a given labeling $\ell_i, i \in 1, \ldots, n$ is compatible with $\hat{\pi}_{2\Delta}$ is equivalent to checking the following set of constraints:

$$\exists \psi_2 \text{ s.t. } \ell_i h_{2,i}^\intercal \psi_2 \geq 1 \quad \forall i \in 1, \ldots, n \tag{13}$$

Given a particular labeling, the existence of a ψ_2 that satisfies (13) can be proven or disproven in polynomial time using a linear program solver (see, for example, Megiddo 1987 and references therein). The existence of such a ψ_2 implies a compatible τ given by $\tau(h_2) = \operatorname{sgn}(h_2^\intercal \psi_2)$ that produces labeling $\ell_1, \ldots, \ell_n$ when applied to the stage 2 data.

To find all possible feasible labelings, we formulate the following mixed integer linear program with indicator constraints

$$\begin{aligned} &\min_{\ell_1, \ell_2, \ldots, \ell_n, \psi_2} f(\ell_1, \ell_2, ..., \ell_n, \psi_2) \\ \text{s.t. } &\forall i \in 1, \ldots, n, \;\; \ell_i \in \{-1, 1\} \\ &\qquad h_{2,2,i}^\intercal \psi_2 \geq 1 \qquad \text{if } \ell_i = 1 \\ &\qquad h_{2,2,i}^\intercal \psi_2 \leq -1 \quad \text{if } \ell_i = -1 \\ &\psi_2 \in \mathbb{R}^{p_2} \end{aligned}$$

[2] In the field of mathematical programming, the term "indicator constraint" is used for a constraint that is only enforced when a variable takes on a particular value, e.g. when an indicator variable is 1. (A better term might be "conditional constraint.")

and find all feasible solutions. Note that exactly one of the constraints involving h_{2i} is enforced for a particular value of ℓ_i. We present the feasibility problem as a minimization because it is the natural form for modern optimization software packages like CPLEX, which are capable of handling both the integer constraints on ℓ_i and the indicator constraints on ψ_2. Note that if we simply want to recover the feasible ℓ_i then the choice of f does not matter, and we may choose $f = 0$ for simplicity and efficiency in practice. CPLEX is capable of enumerating *all* feasible solutions efficiently (the examples considered in this paper take less than one minute to run on a laptop with 8GB DDR3 RAM and a 2.67GHz dual core processor). If we wanted to also recover the maximum margin separators for the feasible labelings, for example, we could use the quadratic objective $f = \|\psi_2\|^2$.

Let $\tilde{\mathcal{F}}(\hat{\pi}_{2\Delta})$ denote the collection of feasible decision rules defined by $\text{sgn}(h_{2,2}^{\intercal}\psi_2)$ for each feasible ψ_2. Then for any $h_1 \in \mathbb{R}^{p_1}$

$$\hat{\pi}_{1\Delta}(h_1) = \bigcup_{\tau_2 \in \tilde{\mathcal{F}}(\hat{\pi}_{2\Delta})} \hat{\pi}_{1\Delta}(h_1, \tau_2). \tag{14}$$

Note that $\tilde{\mathcal{F}}(\hat{\pi}_{2\Delta})$ does not depend on the vector h_1 and hence only needs to be computed once for a given dataset.

5 Examples

5.1 Nefazodone study

In this section we illustrate the estimation of a static set-valued decision rule for a single decision point with two competing outcomes. The data are from the initial (12 week) phase of a multicenter longitudinal study comparing three treatment combinations for chronic depression [Keller et al., 2000]. A total of 681 subjects were randomly assigned with equal probability to nefazodone only (Drug), cognitive behavioral therapy only (CBT), or a combination of the two (Drug+CBT). CBT requires up to twice-weekly on-site visits to the clinic and thus, relative to Drug, CBT represents a substantial time and monetary burden on patients. Hence, an important question is which patients are likely to benefit from CBT beyond Drug only on one or more outcomes. To focus on this question and simplify our exposition, we consider only the treatments Drug and Drug+CBT.

The primary outcome for the study was depression as measured by the 24-item Hamilton Rating Scale for Depression (HRSD) where lower scores signify a healthier state. However, nefazodone is associated with fatigue and lack of physical coordination and thus physical functioning represents an important competing outcome to depression. Physical functioning is quantified in this study using the physical functioning factor score in the Medical Outcomes Study 36-Item Short Form Health Survey (PF). PF was measured at baseline and at 12 weeks and we let Z denote the 12 week measurement. HRSD was measured at baseline and weeks 1, 2, 3, 4, 6, 8, 10, and 12. Let Y_j denote a patients HRSD at week j. To reduce variability and to capture patient improvement over the duration of the study, we define the outcome Y to be the least squares slope of $Y_0, Y_1, \ldots, Y_{12}$ on the observation times $j = 0, 1, \ldots, 12$. For patients missing HRSD measurements Y was computed using the least squares slope of the observed measurements on the observed measurement times.

Of the 681 patients enrolled in the study, 226 were assigned to Drug while 227 were assigned to Drug+CBT. PF was not measured on all patients so we use a subset of 164 patients assigned to Drug and 172 patients with Drug+CBT with complete PF measurements. There was no missingness in baseline covariates. In order to estimate the ideal decision rule derived in Section 3, we modeled the conditional expectations $\mathbb{E}(Y|H = h, A = a)$ and $\mathbb{E}(Z|H = h, A = a)$ using the working models of the form given in (2) and (3). There were a large number of covariates collected at baseline and we constructed our models based on clinician input and exploratory data analysis. Typical regression diagnostics for linear regression [e.g., Cook and Weisberg, 1999] suggest that the models fit the data reasonably well. The covariates included in the model for depression (outcome Y) were the subject's baseline Hamilton depression score (`hamd`); role functioning physical factor score (a measure of the ability to perform physical related roles) (`rolfun`); the assigned treatment (Drug was coded as -1 and Drug+CBT was coded as 1)(`trt`); and the interactions `trt`*`hamd` and `trt`*`rolfun`. The covariates included in the physical functioning model were the subject's baseline physical functioning factor score (`phyfun`); patient gender (`gender`); sleep score (a measure of the subject's quality of sleep) (`slpsc`); overall general health perception score (`genhel`); role functioning score (`rolfun`); age of onset of depression (`mdage`); presence of dysthemia (`dyst`); the assigned treatment (`trt`), and the interactions `trt`*`slpsc` and `trt`*`phyfun`. Tables 1 and 2 display the fitted parameters for each model.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	0.2867	0.2158	1.33	0.1848
hamd	0.0325	0.0074	4.41	0.0000
rolfun	-0.0009	0.0009	-1.01	0.3135
trt	0.1133	0.2158	0.53	0.5998
rolfun*trt	0.0018	0.0009	2.01	0.0452
hamd*trt	0.0011	0.0074	0.14	0.8858

Table 2: Summary of the fitted coefficients for depression model.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	35.6607	4.8319	7.38	0.0000
gender	-3.4435	1.5851	-2.17	0.0305
slpsc	-0.0979	0.3481	-0.28	0.7786
phyfun	0.6198	0.0442	14.01	0.0000
genhel	0.1384	0.0413	3.35	0.0009
rolfun	-0.0436	0.0206	-2.12	0.0349
mdage	-0.1236	0.0583	-2.12	0.0347
dyst	-3.8610	1.4859	-2.60	0.0098
trt	11.3895	3.8200	2.98	0.0031
slpsc*trt	-0.8737	0.3443	-2.54	0.0116
phyfun*trt	-0.0714	0.0365	-1.96	0.0511

Table 3: Summary of the fitted coefficients for physical functioning model.

In what follows we use $\Delta_Y = .25$ as a clinically meaningful difference for depression which translates into a change of 4 units in a subject's depression score over 12 weeks. HRSD is typically categorized into one of five severity categories, four units roughly corresponds to moving one of these categories. We use $\Delta_Z = 5$ which corresponds to a 5% change on the scale PF is measured. It is important to note that these thresholds have been chosen here primarily for illustrative purposes. Using the foregoing values of Δ_Y and Δ_Z, we estimated the ideal decisions using the methods described in Section 3. To get a sense of the estimated set-valued decision rule we approximated the estimated decision rule with a decision tree. Figure 4 displays the estimated ideal decision rule as approximated using a decision tree. Note, 'high','medium' and 'low' values were used instead of actual scores for plot clarity. Drug+CBT was always included in the set of recommended treatments but for patients with low role functioning (`rolfun`) and low sleep scores (`slpsc`) there a negligible treatment effect and Drug only may not be significantly different than Drug+CBT. Another useful display of the set valued decision rule is to plot the estimated contrasts $2h_{1,2}^T\hat{\psi}_Y$ and $2h_{1,2}^T\hat{\psi}_Z$ against each other and to label the regions where the decision rule changes. This plot is shown in Figure 5.

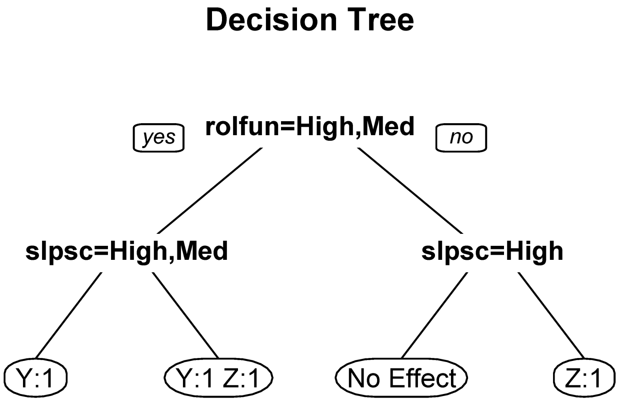

Figure 4: A decision tree approximating the estimated ideal decision rule for the nefazodone study. The leaves of the tree indicate the optimal treatment (1 for combination or -1 for drug) along with which outcome (Y for depression or Z for physical functioning) the subject would see a clinically significant change in.

The primary analysis of the depression study found that the Drug+CBT was the most effective [Keller et al., 2000] and the results in Figures 4 and 5 are consistent with this analysis. Almost always, the combination treatment was recommend when considering depression and physical functioning as the competing outcomes. As seen in Figure 4, only 5 subjects were assigned the drug treatment as their ideal treatment with the remaining subjects being assigned either the combination treatment or no treatment. Because of this, the decision tree in Figure 4 only assigns future subjects to the combination treatment or no treatment. Additionally, it provides information about which outcome the subject would likely see clinically significant results in if they were to follow these decisions. Note that the `slpsc*trt` and `rolfun*trt` interactions were both found significant in the models and it is at these variables where the splits in the tree were made.

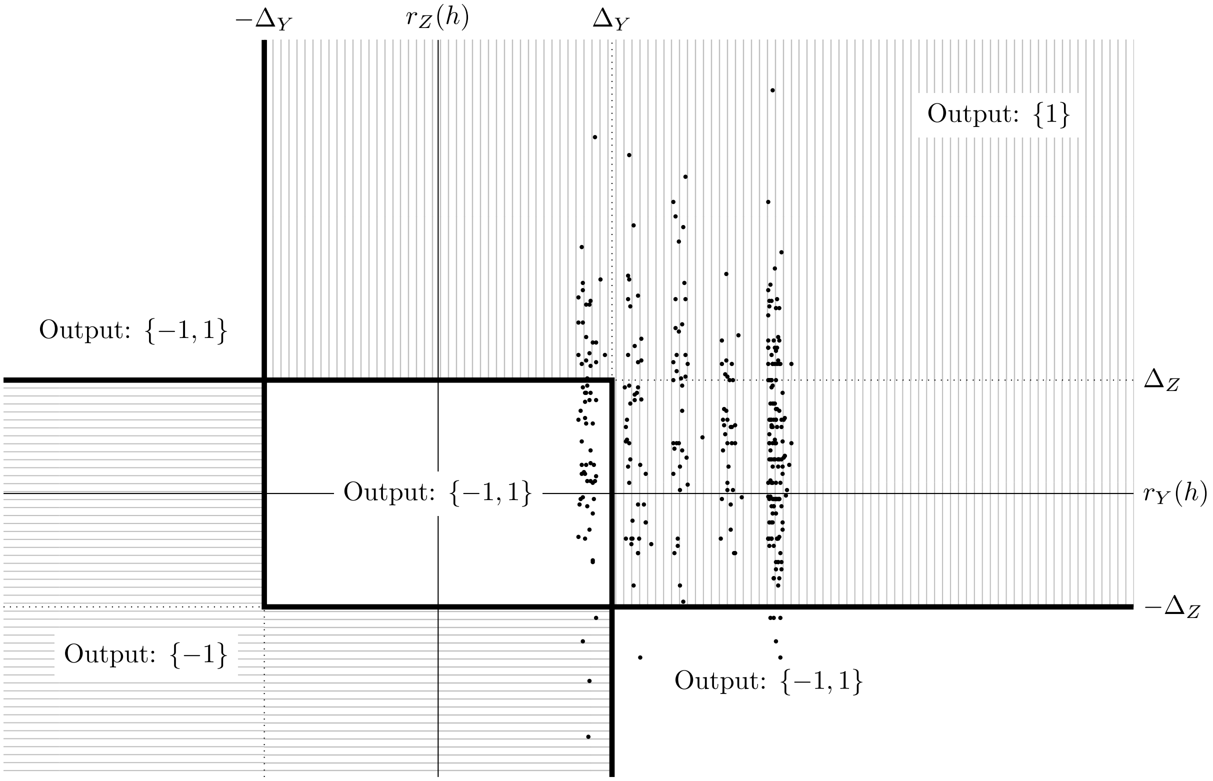

Figure 5: Diagram showing how the output of $\pi^{\text{Ideal}}(h)$ depends on Δ_Y and Δ_Z, and on the location of the point $(r_Y(h), r_Z(h))$.

5.2 CATIE

We now consider the application of our method to data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia study. The CATIE study was designed to compare sequences of antipsychotic drug treatments for the care of schizophrenia patients. The full study design is quite complex [Stroup et al., 2003]; we will make several simplifications in order to more clearly illustrate the potential of the method presented here. CATIE was an 18-month sequential randomized trial that was divided into two main phases of treatment. Upon entry into the study, most patients began "Phase 1," in which they were randomized to one of five possible treatments with equal probability: olanzapine, risperidone, quetiapine, ziprasidone, or perphenazine. As they progressed through the study, patients were given the opportunity at each monthly visit to discontinue their Phase 1 treatment and begin "Phase 2" on a new treatment. The set of possible Phase 2 treatments depended on the reason for discontinuing Phase 1 treatment. If the Phase 1 treatment was deemed to produce unacceptable side-effects, they entered the *tolerability arm* and their Phase 2 treatment was chosen uniformly randomly from the set {olanzapine, risperidone, quetiapine, ziprasidone}. If the Phase 1 treatment was deemed to be ineffective at reducing symptoms, they entered the *efficacy arm* and their Phase 2 treatment was chosen randomly as follows: clozapine with probability 1/2, or uniformly randomly from the set {olanzapine, risperidone, quetiapine} with probability 1/2.

Although CATIE was designed to compare several treatments within each arm, there are natural groupings at each stage that allow us to collapse the data in a meaningful way so that we consider only binary treatments and we can therefore directly apply our method as described. In the Phase 2 Tolerability arm, it is natural to compare olanzapine against the other three drugs since it is known a priori to be efficacious, but is also known to cause significant weight gain as a side-effect. In the Phase 2 Efficacy arm, it is natural to compare clozapine against the rest of the potential treatments, both because the randomization probabilities called for having 50% of patients in that arm on clozapine, and because clozapine is substantively different from the other three drugs: it is known to be highly effective at controlling symptoms, but it is also known to have significant side-effects and its safe administration requires very close patient monitoring. In Phase 1, it is natural to compare perphenazine, the only typical antipsychotic, against the other four drugs which are atypical antipsychotics. (This comparison of typical-versus-atypical was in fact an important goal of the CATIE study.)

For our first outcome, Y, we use the Positive and Negative Syndrome Scale (PANSS) which is a numerical representation of the level of psychotic symptoms experienced by a patient [Kay et al., 1987]. A higher value of PANSS reflects the presence of more severe symptoms. PANSS is a well-established measure that we have used in previous work on the CATIE study [Shortreed et al., 2011]. Since having larger PANSS is worse, for our first outcome Y we use 100 minus the percentile of a patient's PANSS at the end of their time in the study. We use the distribution of PANSS at the beginning of the study as the reference distribution for the percentile.

For our second outcome, we use Body Mass Index (BMI), a measure of obesity. Weight gain is an important and problematic side-effect of many antipsychotic drugs [Allison et al., 1999]. Since in this population having a larger BMI is worse, for our second outcome Z we use 100 minus the percentile of a patient's BMI at the end of their time in the study. Again, we use the distribution of BMI at the beginning of the study as the reference distribution for the percentile.

In all of our models, we include two baseline covariates. The first, `td`, is a dummy variable indicating if a patient has "tardive dyskinesia," which is a motor side-effect that can be caused by previous treatment. The second, `exacer`, is a dummy variable indicating that a patient has been recently hospitalized, thus indicating an exacerbation of his or her condition. These do not interact with treatment.

For our covariates h_2 that interact with treatment, we choose the patients most recently recorded PANSS score percentile in our model for PANSS, and the most recently recorded BMI percentile in our model for BMI. These percentiles were shifted by -50 so that a patient with at the median has $h_2 = 0$. This was done so that in each model, the coefficient for the main effect of treatment can be directly interpreted as the treatment effect for a patient with median PANSS (resp. BMI). Treatments were coded $1, -1$. For both outcomes we chose 5 percentile points as our indifference range, so $\Delta_Y = \Delta_Z = 5$.

5.2.1 Phase 2 Tolerability

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	55.6979	2.0335	27.3898	0.0000
`td`	-3.5892	3.8915	-0.9223	0.3571
`exacer`	0.8697	3.2249	0.2697	0.7876
`panss`	0.6213	0.0581	10.7015	0.0000
`olan`	3.2705	1.6885	1.9370	0.0054
`panss*olan`	-0.0136	0.0583	-0.2326	0.8162

Table 4: Summary of the fitted coefficients for PANSS outcome, Phase 2 Tolerability arm. $N = 295$.

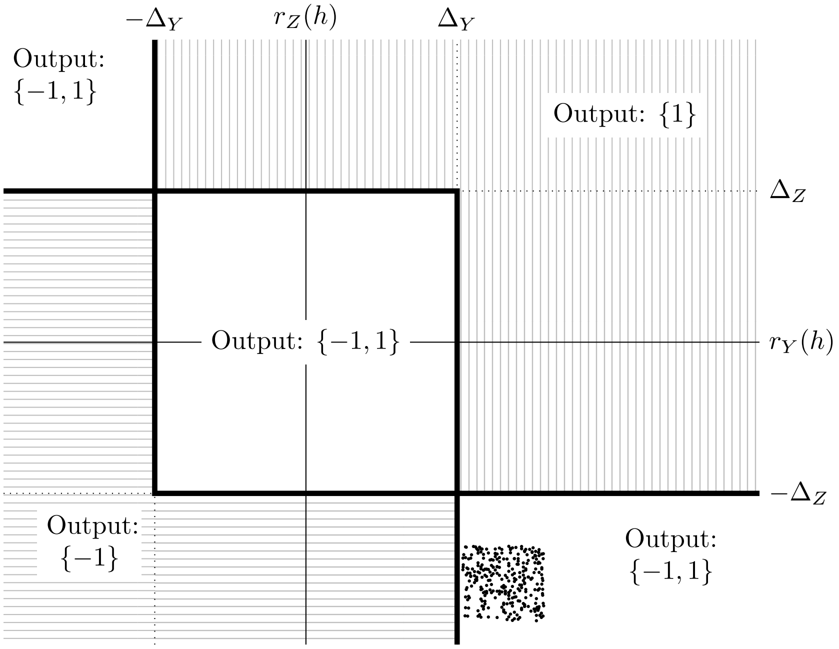

Figure 6: Diagram showing how the output of $\pi^{\text{Ideal}}(h)$ depends on Δ_Y and Δ_Z, and on the location of the point $(r_Y(h), r_Z(h))$, for the Phase 2 Tolerability arm.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	47.7079	0.8138	58.6223	0.0000
td	0.7497	1.5619	0.4800	0.6316
exacer	-0.9157	1.2952	-0.7070	0.4801
bmi	0.9166	0.0228	40.1616	0.0000
olan	-3.9836	0.6708	-5.9383	0.0000
bmi*olan	-0.0124	0.0228	-0.5464	0.5852

Table 5: Summary of the fitted coefficients for BMI outcome, Phase 2 Tolerability arm. $N = 295$.

Tables 4 and 5 show the models estimated from the Phase 2 tolerability data. As expected, olanzapine appears to be benificial if one considers the PANSS (Y) outcome, but detrimental if one considers the BMI (Z) outcome. This is borne out in Figure 6, where we see that the predictions of (r_Y, r_Z) for all of the patient histories in our dataset fall in the lower-right region of the plot, where both treatments are recommended because they conflict with each other according to the two outcomes.

5.2.2 Phase 2 Efficacy

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	54.7307	4.4225	12.3756	0.0000
td	1.1844	7.9962	0.1481	0.8828
exacer	-3.0871	6.9329	-0.4453	0.6580
panss	0.6363	0.1299	4.898	0.0000
cloz	9.2920	3.7722	2.463	0.0173
panss*cloz	0.0220	0.1312	0.1673	0.8678

Table 6: Summary of the fitted coefficients for PANSS outcome, Phase 2 Efficacy arm.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	50.7367	1.7384	29.1863	0.0000
td	-5.2649	3.0542	-1.7238	0.0916
exacer	-2.1386	2.8634	-0.7469	0.4586
bmi	0.9277	0.0507	18.2857	0.0000
cloz	-1.1109	1.3582	-0.8179	0.4173
bmi*cloz	-0.0592	0.0525	-1.1272	0.2650

Table 7: Summary of the fitted coefficients for BMI outcome, Phase 2 Efficacy arm. $N = 56$

Tables 6 and 7 show the models estimated from the Phase 2 efficacy data. As expected, clozapine appears to be beneficial if one considers the PANSS (Y) outcome. Furthermore, there is weak evidence that clozapine is detrimental if one considers the BMI (Z) outcome. This is borne out in Figure 7, where we see that the predictions of (r_Y, r_Z) for all of the patient histories in our dataset are to the right of $r_Y = \Delta_Y$, indicating that clozapine is predicted to be the better choice for all patients in the dataset when considering only the PANSS outcome. Furthermore, for most of these, clozapine is not significantly worse than the other (aggregate) treatment according to BMI; thus for most of the histories only clozapine (i.e. $\{1\}$ would be recommended. We found that for patients with a BMI covariate greater than about 24 (i.e. those among the top best 25 percent according to BMI[3]), however, clozapine is predicted to perform clinically significantly

[3] Recall the negative coding (higher percentiles are better) and the shift by 50: It is the patients whose BMI is better than the 74th percentile who are recommended both treatments $\{-1, 1\}$.

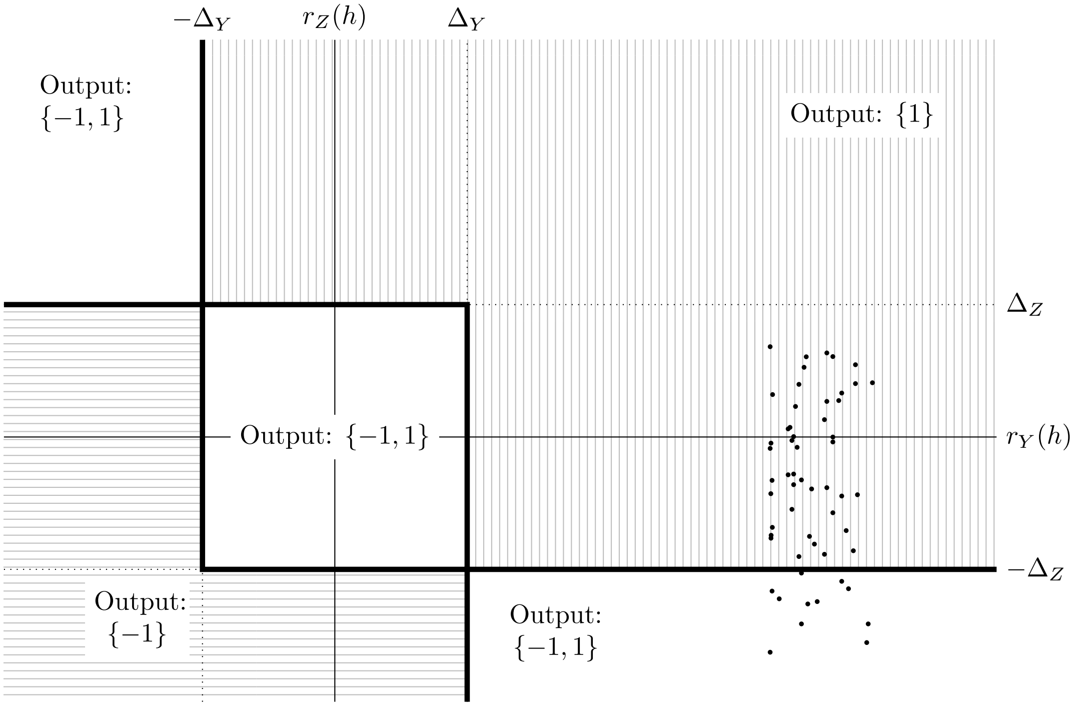

Figure 7: Diagram showing how the output of $\pi^{\text{Ideal}}(h)$ depends on Δ_Y and Δ_Z, and on the location of the point $(r_Y(h), r_Z(h))$, for the Phase 2 Efficacy arm. $N = 56$.

worse according to the BMI outcome, and both treatments (i.e. $\{-1,1\}$) would be recommended for these patients.

5.2.3 Phase 1

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	57.3576	1.0382	55.2486	0.0000
td	-5.8840	2.0415	-2.8823	0.0004
exacer	1.1234	1.6471	0.6821	0.4954
panss	0.5332	0.0318	16.7574	0.0000
perp	-2.6691	0.9505	-2.8081	0.0051
panss*perp	0.0778	0.0317	2.4531	0.0143

Table 8: Example summary of the fitted coefficients for PANSS outcome, Phase 1, based on a randomly chosen feasible decision rule for Phase 2. $N = 974$

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	49.0622	0.5084	96.5089	0.0000
td	1.2004	1.0069	1.1922	0.2335
exacer	-2.7812	0.8175	-3.4022	0.0007
bmi	0.9134	0.0163	55.2402	0.0000
perp	1.8266	0.4659	3.9197	0.0001
bmi*perp	-0.0250	0.0163	-1.5388	0.1242

Table 9: Example summary of the fitted coefficients for BMI outcome, based on a randomly chosen feasible decision rule for Phase 2. $N = 974$.

We now consider Phase 1. Recall that given any history h_1 at Phase 1, our predicted values (r_Y, r_Z) for that history depend not only on the history itself but on the future decision rule that will be followed subsequently. For illustrative purposes, Tables 8 and 9 show the models estimated from the Phase 1 data assuming a particular feasible decision rule for Phase 2 chosen from the $61,659$ feasible Phase 2 decision rules enumerated by our algorithm. (The estimated coefficients would be different had we used a different Phase 2 decision rule.) For this particular future decision rule, perphenazine performs somewhat worse according to PANSS than the atypical antipsychotics, and somewhat better according to BMI.

Whereas for the Phase 2 analyses we showed plots of different (r_Y, r_Z) for different histories, for Phase 1, we will show different (r_Y, r_Z) for a *fixed* history at Phase 1 as we vary the Phase 2 decision rule. Recall that our treatment recommendation for Phase 1 is the union over all feasible future decision rules of the treatments recommended for each future decision rule. Figure 8 shows the possible values of (r_Y, r_Z). From Figure 8, we can see that for some future decision rules only treatment -1 is recommended, but for others the set $\{-1, 1\}$ is recommended. Taking the union, we recommend the set $\{-1, 1\}$ for this history at Phase 1.

6 Discussion

We proposed set-valued dynamic treatment regimes as a method for adapting treatment recommendations to the evolving health status of a patient in the presence of competing outcomes. Our proposed methodology deals with the reality that there is typically no universally good treatment for chronic illnesses like depression or schizophrenia by identifying when a trade-off between effectiveness and side-effects must be made.

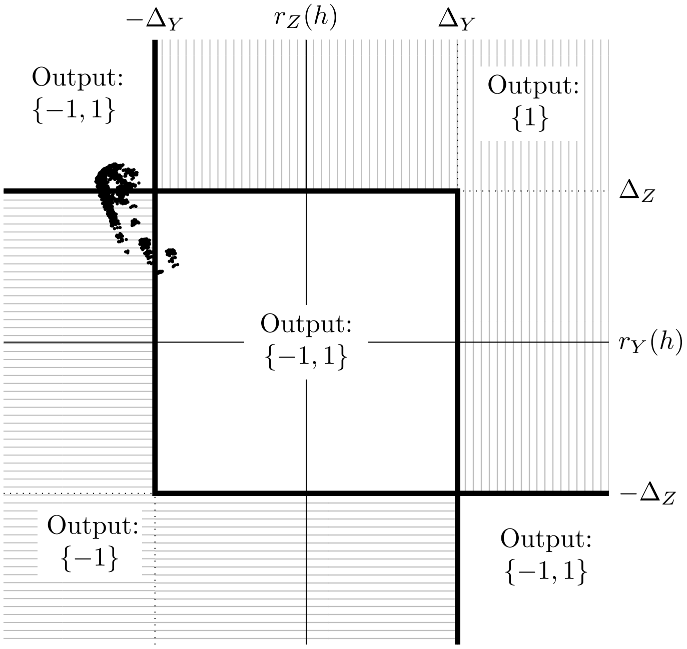

Figure 8: Diagram showing how the output of $\pi^{\text{Ideal}}(h)$ depends on Δ_Y and Δ_Z, and on the location of the point $(r_Y(h), r_Z(h))$, for Phase 1, at history $\texttt{panss} = -25.5$,$\texttt{bmi} = -15.6$).

Although computation of the set-valued dynamic treatment regimes requires solving a difficult enumeration problem, we offered an efficient algorithm that makes use of existing linear mixed integer programming software packages. We demonstrated the use of our method using data from one-stage and two-stage randomized clinical trials.

Our proposed methodology avoids the construction of composite outcomes, a process which may be undesirable: constructing a composite outcome requires combining outcomes that are on different scales, the 'optimal trade-off' between two (or more) outcomes is likely to be patient-specific, and the assumption that a linear trade-off is sufficient to describe all possible patient preferences may be unrealistic.

There are a number of directions in which this work can be extended. The appendix provides an extension to the case with two decision points but an arbitrary number of treatment choices available at each stage. Interestingly, our enumeration problem is closely related to *transductive learning*, a classification problem setting where only a subset of the available training data is labeled, and the task is to predict labels at the unlabeled points in the training data. By finding a minimum-norm solution for ψ subject to our constraints, we could produce the transductive labeling that induces the maximum margin linear separator. In essence, our algorithm would then correspond to a linear separable transductive support vector machine (SVM)

[Cortes and Vapnik, 1995]. This observation leads to a possible criterion for evaluating feasible decision rules: we hypothesize that the greater the induced margin, the more "intuitive" the decision rule, because large-margin decision rules avoid giving very similar patients different treatments. If the number of feasible future decision rules becomes impractically large, we may wish to keep only the most "separable" ones when computing the union at the first stage. We are currently pursuing this line of research.

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A Multiple Treatments

To develop our method for the binary treatment case, we considered working models of the form $Q_t(h_t, a_t) = h_{t,1}^\intercal \beta_t + a_t h_{t,2}^\intercal \psi_t$, and we defined our estimated optimal treatment for history h_t to be $\hat{\pi}_t(h_t) = \arg\max_{a_t \in \{-1,1\}} \hat{Q}(h_t, a_t)$. If there are more than two levels of treatment (suppose a_t belongs to a discrete set $\mathcal{A}_t$) we define estimated working models of the form

$$\hat{Q}_t(h_t, a_t) = h_{t,1}^\intercal \hat{\beta}_t + \phi(a_t, h_{t,2})^\intercal \hat{\psi}_t \tag{15}$$

where the vector-valued function ϕ describes an arbitrary encoding of a_t along with any desired interactions between the encoding and $h_{t,2}$. For example, if $\mathcal{A}_t = \{1, 2, 3\}$ and $h_{t,2}$ is a scalar, we might use

$$\phi(a_t, h_{t,2}) = \begin{cases} (0, 0, 0, 0)^\intercal & \text{if } a_t = 1 \\ (1, 0, h_{t,2}, 0)^\intercal & \text{if } a_t = 2 \\ (0, 1, 0, h_{t,2})^\intercal & \text{if } a_t = 3 \end{cases} \tag{16}$$

to produce a model that incorporates a main effect of treatment as well as an interaction between treatment and $h_{t,2}$. The choice of how to encode factors and interactions has been well-studied [Wu et al., 2000]. Regardless of the specific choice of encoding, our estimated DTR is $\hat{\pi}_t(h_t) = \arg\max_{a_t \in \mathcal{A}_t} \hat{Q}(h_t, a_t)$.

A.1 Producing the Set-Valued Decision Rule

In order to identify the set of treatments that should be recommended for a particular h_t, we consider all pairs of treatments and identify those which are never eliminated in any pairwise comparison according to our definition of 'clincial significance.' Continuing our example, if for a particular h_t we find that considering 1 and 2 recommends the set $\{1, 2\}$ and that considering 1 and 3 recommends the set $\{1\}$, then we would include treatment 1 in our recommended set for h_t. Note that we can also infer that 3 would *not* be recommended, since in a pairwise comparison with 1 it is eliminated.

A.2 Enumerating the Feasible Decision Rules

To construct the MIP describing the feasible decision rules, we introduce $n \times |\mathcal{A}_t|$ indicator variables $\alpha_{i,j}$ that indicate whether $\hat{\pi}(h_t^{(i)}) = j$ or not. We then impose the following constraints:

$$\forall i \in 1...n,\ j \in 1...|\mathcal{A}_t|,\ \alpha_{i,j} \in \{0, 1\} \tag{17}$$

$$\forall i \in 1...n,\ \sum_j \alpha_{i,j} = 1 \tag{18}$$

$$\forall i \in 1...n,\ \forall j \in 1...|\mathcal{A}_t|,\ \alpha_{i,j} = 1 \implies \forall k \neq j,\ (\phi(h_t^{(i)}, j) - \phi(h_t^{(i)}, k))^\intercal \psi_2 \geq 1. \tag{19}$$

Constraints (17) ensure that the indicator variables for the actions are binary. Constraints (18) ensure that, for each example in our dataset, exactly one action indicator variable is on. The indicator constraints in (19) ensure that if the indicator for action j is on for the ith example, then weights must satisfy $j =$

$\arg\max_a \phi(s^i, a)^\intercal w$. Note that the margin condition (i.e. having the constraint be ≥ 1 rather than ≥ 0) avoids a degenerate solution with $\psi_2 = \mathbf{0}$.

The above constraints ensure that the $\alpha_{i,j}$ define a treatment rule that can be represented as an $\arg\max$ in the given covariate space. Imposing the additional constraint that the treatment rule defined is compatible with a given set-valued treatment rule $\tilde{\pi}$ is now trivial:

$$\forall i \in 1...n, \quad \sum_{j \in \tilde{\pi}(h^{(i)})} \alpha_{i,j} = 1. \tag{20}$$

Constraints (20) ensure that the indicator that turns on for the ith example in the data must be one that indicates an action already present in $\tilde{\pi}(h^{(i)})$.

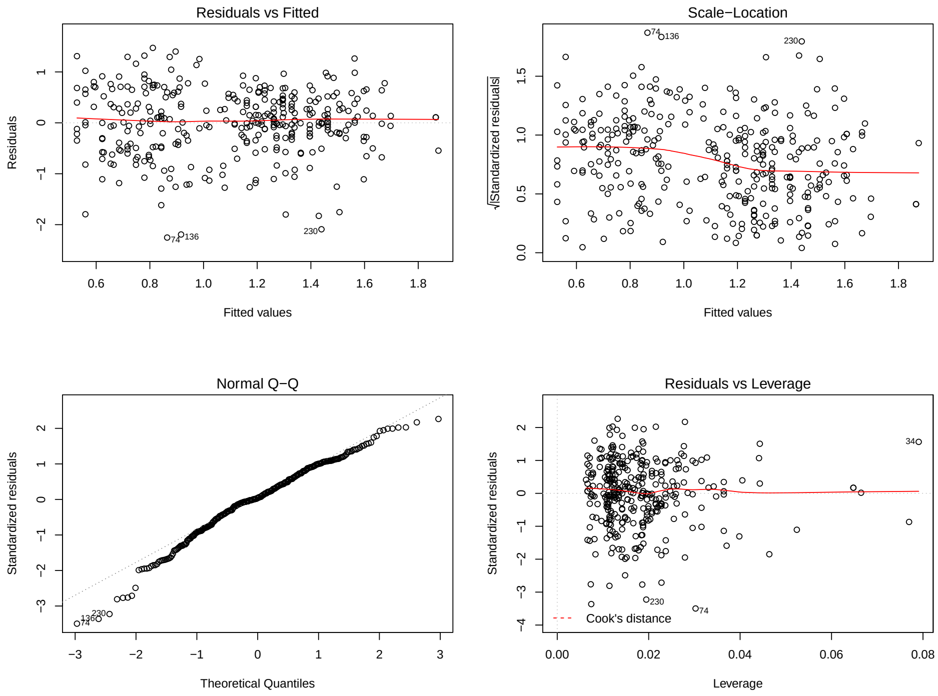
Using the approaches developed in Sections A.1 and A.2, an estimation procedure analogous to that described in Section 4 immediately follows.

B Regression Diagnostics

B.1 Nefazodone study

Depression

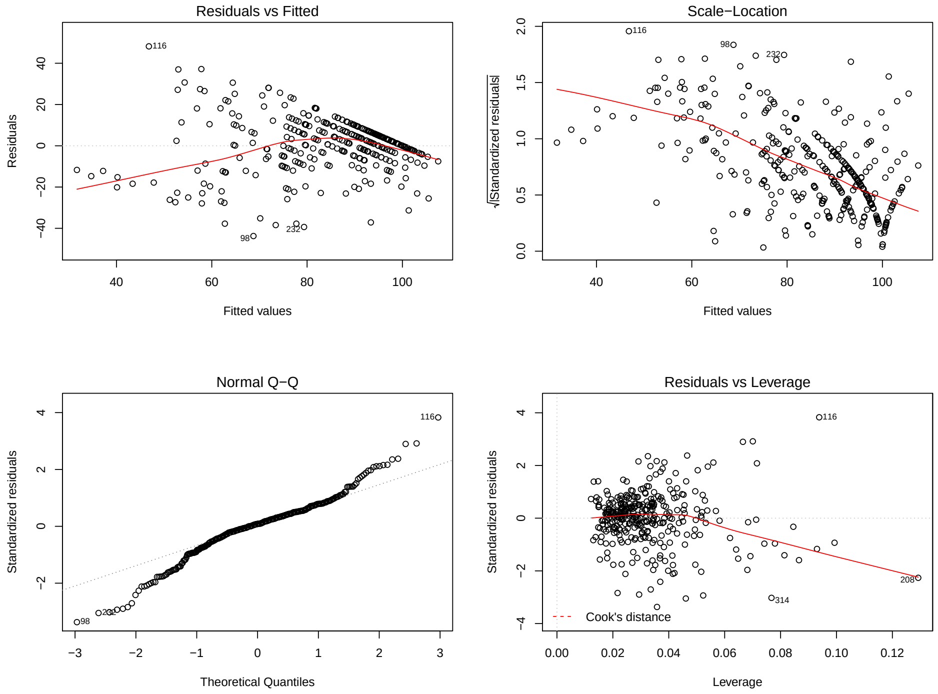
```
Residuals:
     Min       1Q   Median       3Q      Max
-2.25326 -0.35043  0.02561  0.46046  1.47199


Coefficients:
               Estimate Std. Error t value Pr(>|t|)
(Intercept)   0.2867221  0.2157694   1.329   0.1848
HAMDTOT       0.0324713  0.0073585   4.413 1.38e-05 ***
ROLFUN       -0.0009138  0.0009052  -1.009   0.3135
RAND          0.1133281  0.2157694   0.525   0.5998
ROLFUN:RAND   0.0018196  0.0009052   2.010   0.0452 *
HAMDTOT:RAND  0.0010579  0.0073585   0.144   0.8858
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1


Residual standard error: 0.6544 on 330 degrees of freedom
Multiple R-squared: 0.1969,Adjusted R-squared: 0.1847
F-statistic: 16.18 on 5 and 330 DF,  p-value: 2.835e-14
```



Physical Functioning

```
Residuals:
    Min      1Q  Median      3Q     Max
-43.741  -5.730   1.100   6.801  48.197


Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 35.66068    4.83187   7.380 1.34e-12 ***
GENDER2     -3.44352    1.58505  -2.172 0.030543 *
SLPSC1      -0.09793    0.34809  -0.281 0.778627
PHYFUN       0.61981    0.04425  14.009  < 2e-16 ***
GENHEL       0.13838    0.04132   3.349 0.000906 ***
ROLFUN      -0.04361    0.02059  -2.118 0.034945 *
MD_AGE      -0.12357    0.05826  -2.121 0.034682 *
DYST_YES    -3.86101    1.48587  -2.598 0.009792 **
RAND        11.38947    3.82004   2.982 0.003086 **
```

```
SLPSC1:RAND -0.87366    0.34430  -2.538 0.011633 *

PHYFUN:RAND -0.07143    0.03648  -1.958 0.051116 .

---

Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1


Residual standard error: 13.22 on 324 degrees of freedom

  (1 observation deleted due to missingness)

Multiple R-squared: 0.5556,Adjusted R-squared: 0.5419

F-statistic: 40.51 on 10 and 324 DF,  p-value: < 2.2e-16
```

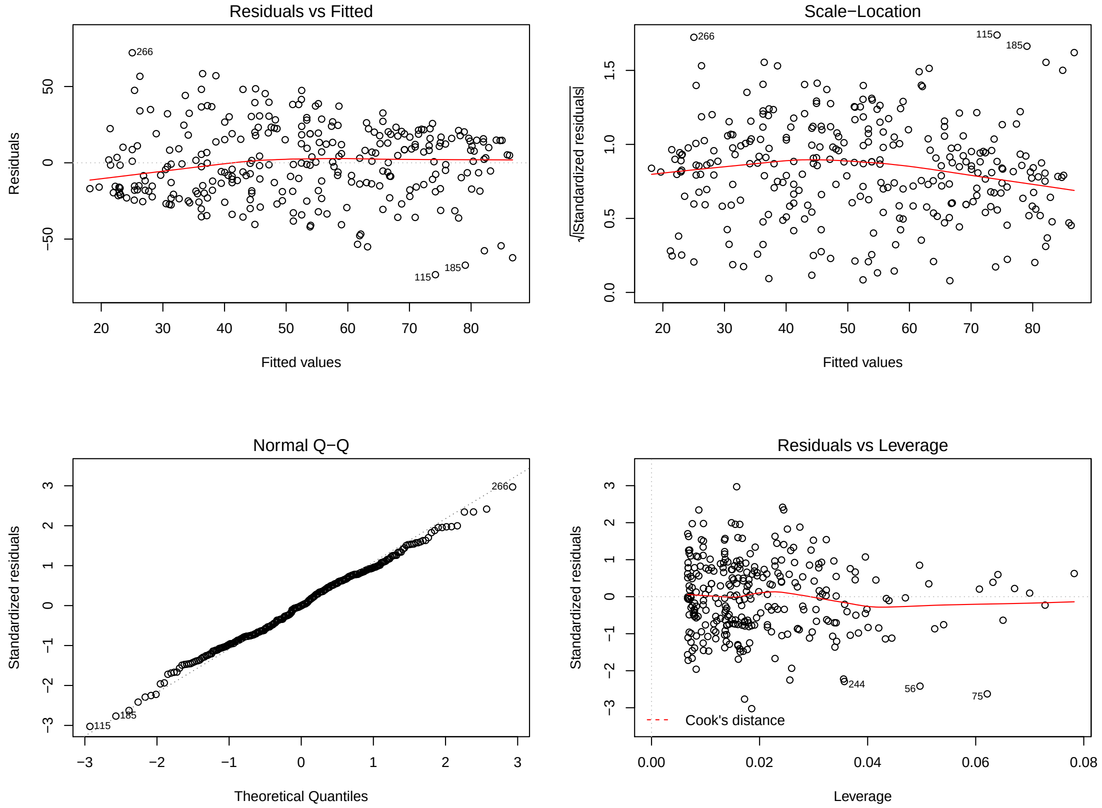


B.2 CATIE

Note that at Phase 1 the regression estimators are non-regular, and that inference in this setting requires additional care as many standard methods are not valid [Laber et al., 2011]. Nonetheless we include the following standard regression diagnostics to give a sense of model fit.

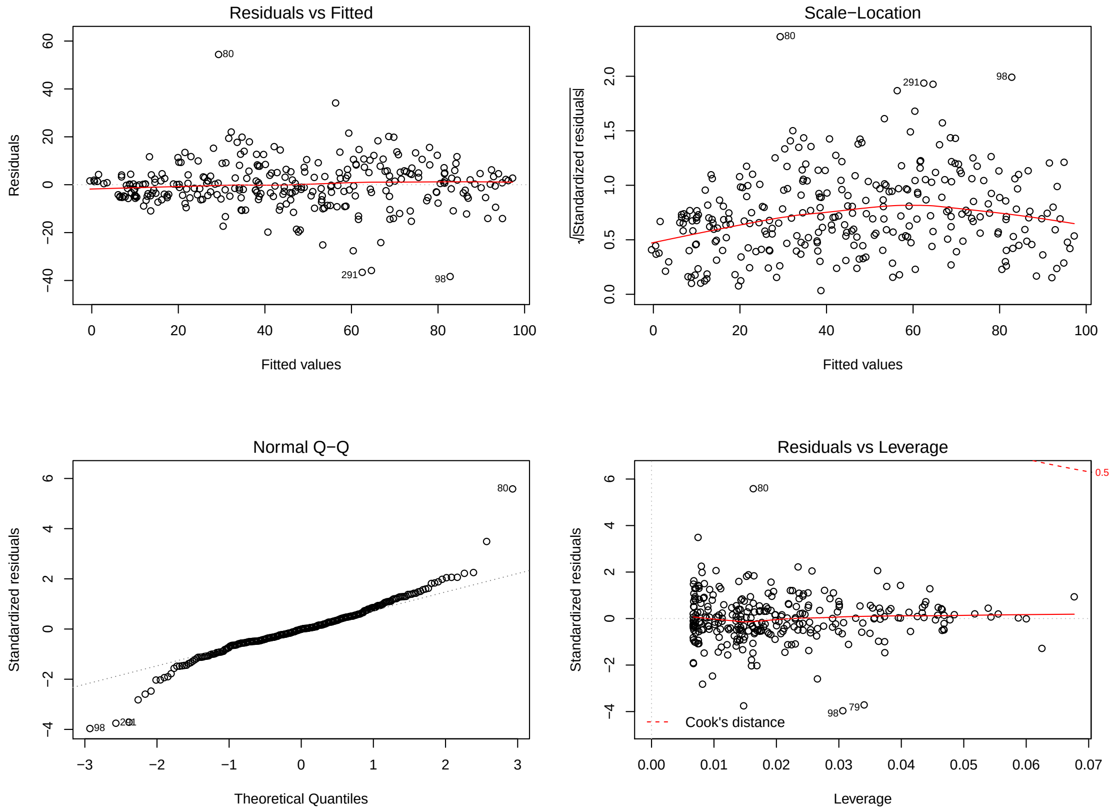
B.2.1 Phase 2 Tolerability: PANSS

```
Residuals:
    Min      1Q  Median      3Q     Max
-73.323 -17.868  -0.176  17.801  72.125

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 55.69794    2.03353  27.390   <2e-16 ***
TD          -3.58917    3.89155  -0.922   0.3571
EXACER       0.86974    3.22493   0.270   0.7876
PANSS        0.62132    0.05806  10.702   <2e-16 ***
OLAN         3.27049    1.68846   1.937   0.0537 .
PANSS:OLAN  -0.01356    0.05829  -0.233   0.8162
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Residual standard error: 24.47 on 289 degrees of freedom
Multiple R-squared: 0.3613,Adjusted R-squared: 0.3503
F-statistic:  32.7 on 5 and 289 DF,  p-value: < 2.2e-16
```



B.2.2 Phase 2 Tolerability: BMI

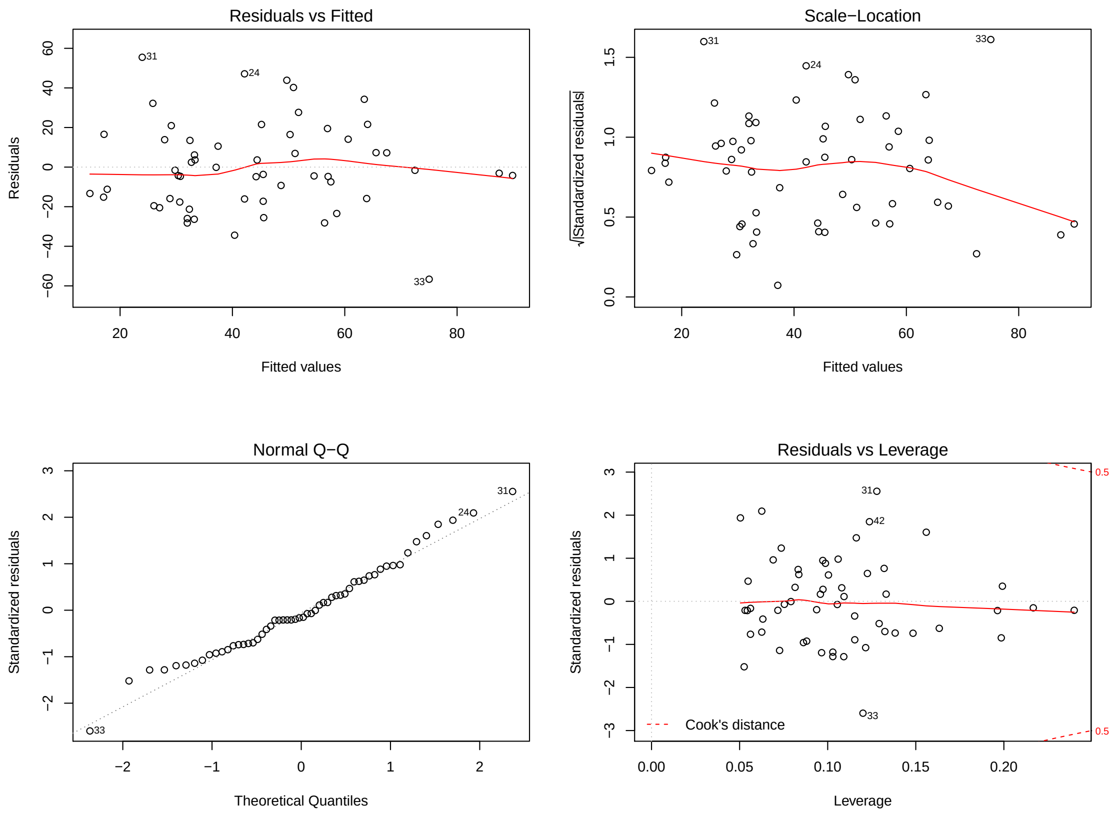
```
Residuals:
    Min      1Q  Median      3Q     Max
-38.343  -4.787  -0.097   4.886  54.400

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 47.70789    0.81382  58.622  < 2e-16 ***
TD           0.74972    1.56186   0.480    0.632
EXACER      -0.91572    1.29519  -0.707    0.480
BMI          0.91663    0.02282  40.162  < 2e-16 ***
OLAN        -3.98360    0.67083  -5.938 8.25e-09 ***
BMI:OLAN    -0.01245    0.02278  -0.546    0.585
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Residual standard error: 9.822 on 289 degrees of freedom
Multiple R-squared: 0.8765,Adjusted R-squared: 0.8744
F-statistic: 410.4 on 5 and 289 DF,  p-value: < 2.2e-16
```



B.2.3 Phase 2 Efficacy: PANSS

```
Residuals:
    Min      1Q  Median      3Q     Max
-56.634 -15.947  -3.404  13.906  55.476
```

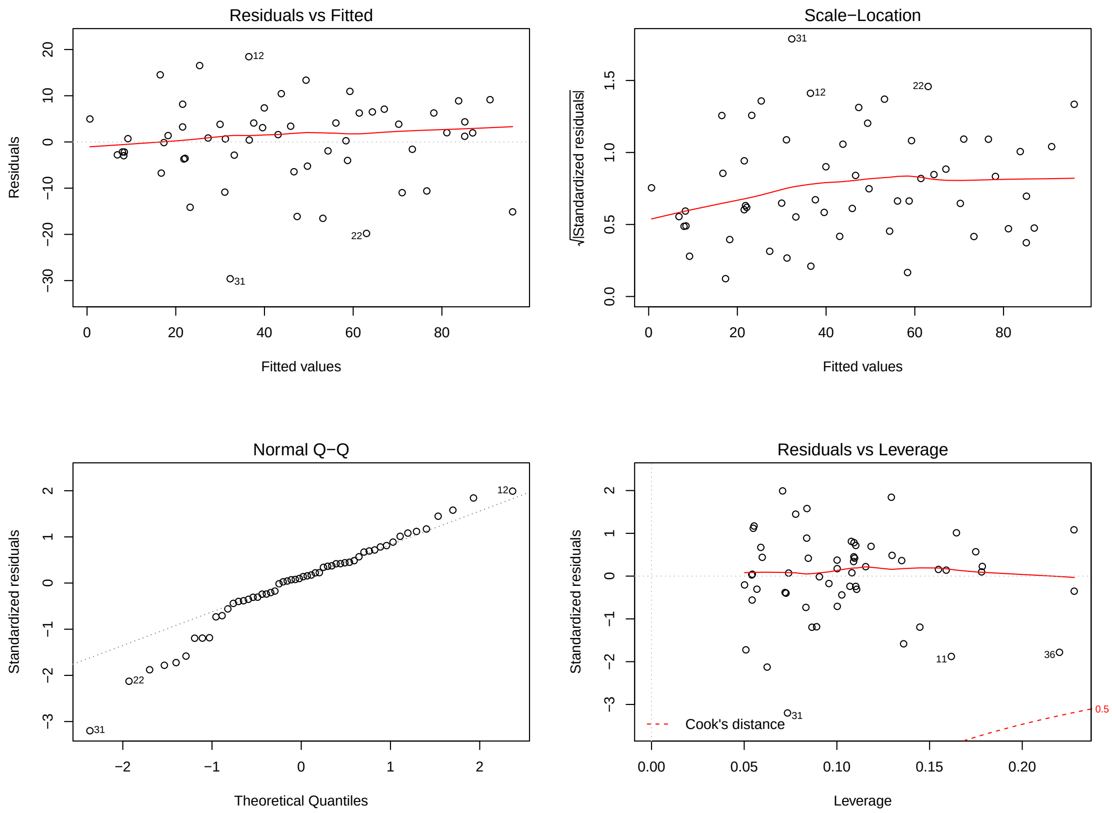
```
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 54.73068    4.42248  12.376  < 2e-16 ***
TD           1.18442    7.99619   0.148   0.8828
EXACER      -3.08713    6.93291  -0.445   0.6580
PANSS        0.63633    0.12991   4.898 1.06e-05 ***
CLOZ         9.29195    3.77220   2.463   0.0173 *
PANSS:CLOZ   0.02196    0.13122   0.167   0.8678
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Residual standard error: 23.25 on 50 degrees of freedom
Multiple R-squared: 0.3782,Adjusted R-squared: 0.316
F-statistic: 6.082 on 5 and 50 DF,  p-value: 0.0001793
```



B.2.4 Phase 2 Efficacy: BMI

```
Residuals:
    Min      1Q  Median      3Q     Max
-29.599  -3.581   1.045   5.294  18.453

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 50.73675    1.73837  29.186   <2e-16 ***
```

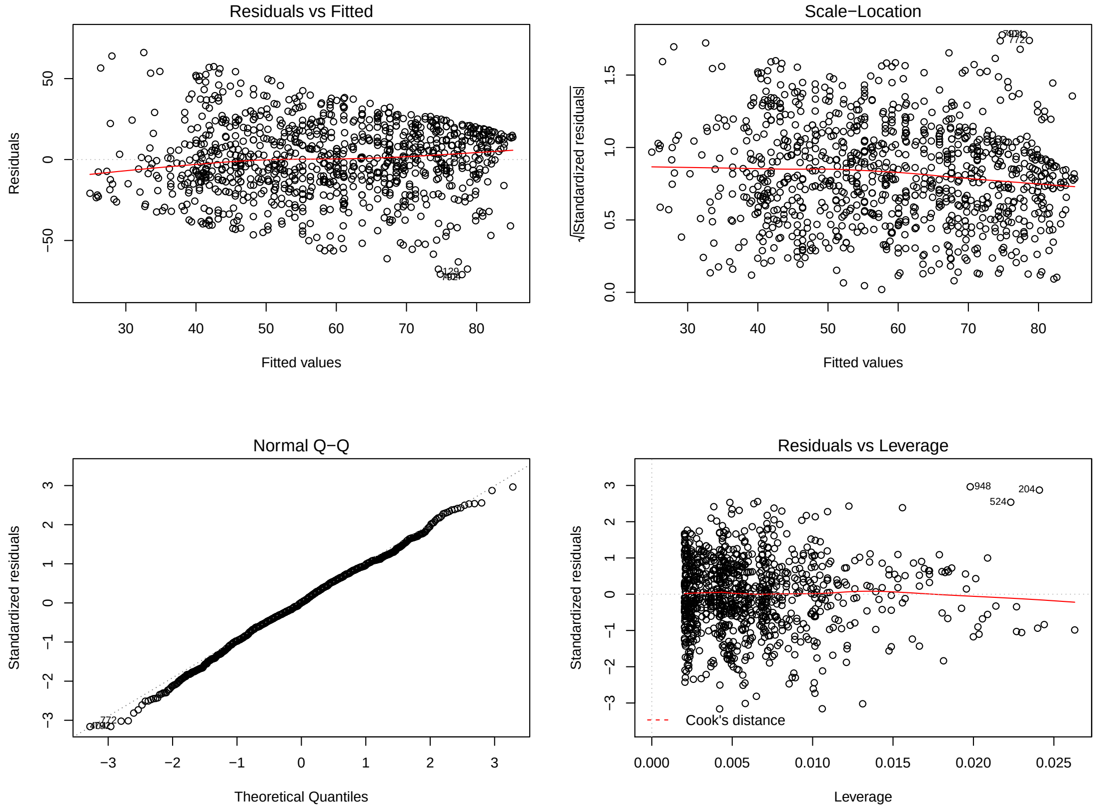
```
TD          -5.26487    3.05415  -1.724   0.0909 .
EXACER      -2.13863    2.86341  -0.747   0.4586
BMI          0.92768    0.05073  18.286   <2e-16 ***
CLOZ        -1.11087    1.35825  -0.818   0.4173
BMI:CLOZ    -0.05915    0.05248  -1.127   0.2650
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Residual standard error: 9.611 on 50 degrees of freedom
Multiple R-squared: 0.8846,Adjusted R-squared: 0.8731
F-statistic: 76.67 on 5 and 50 DF,  p-value: < 2.2e-16
```



B.2.5 Phase 1 PANSS - For a particular feasible Phase 2 decision rule

```
Residuals:
    Min      1Q  Median      3Q     Max
-71.066 -13.755   0.302  15.982  66.103

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 57.35755    1.03817  55.249  < 2e-16 ***
TD          -5.88398    2.04147  -2.882  0.00404 **
EXACER       1.12338    1.64705   0.682  0.49537
PANSS        0.53324    0.03182  16.757  < 2e-16 ***
```

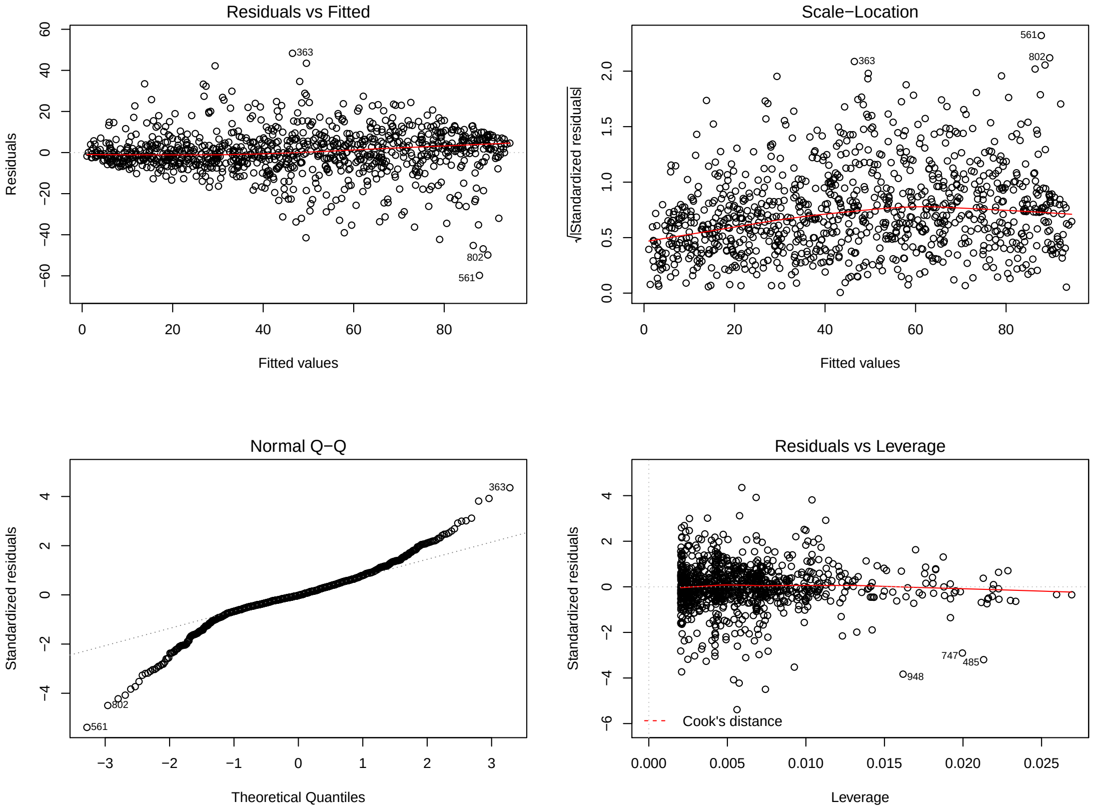
```
PERP        -2.66918    0.95054  -2.808  0.00508 **
PANSS:PERP   0.07784    0.03173   2.453  0.01434 *
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Residual standard error: 22.53 on 969 degrees of freedom
Multiple R-squared: 0.2854,Adjusted R-squared: 0.2817
F-statistic: 77.38 on 5 and 969 DF,  p-value: < 2.2e-16
```



B.2.6 Phase 1 BMI - For a particular feasible Phase 2 decision rule

```
Residuals:
    Min      1Q  Median      3Q     Max
-59.767  -4.776  -0.307   5.721  48.318

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 49.06219    0.50837  96.509  < 2e-16 ***
TD           1.20040    1.00689   1.192 0.233479
EXACER      -2.78115    0.81747  -3.402 0.000696 ***
BMI          0.90136    0.01632  55.240  < 2e-16 ***
PERP         1.82645    0.46597   3.920 9.49e-05 ***
BMI:PERP    -0.02502    0.01626  -1.539 0.124167
---
```

```
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Residual standard error: 11.13 on 969 degrees of freedom
Multiple R-squared: 0.8451,Adjusted R-squared: 0.8443
F-statistic:  1057 on 5 and 969 DF,  p-value: < 2.2e-16
```


Residuals vs Fitted
Residuals
60
40
20
0
−20
−40
−60
363
802
561
0
20
40
60
80
Fitted values
Scale−Location
√|Standardized residuals|
2.0
1.5
1.0
0.5
0.0
561
802
363
0
20
40
60
80
Fitted values
Normal Q−Q
Standardized residuals
4
2
0
−2
−4
363
802
561
−3
−2
−1
0
1
2
3
Theoretical Quantiles
Residuals vs Leverage
Standardized residuals
4
2
0
−2
−4
−6
747
485
948
Cook's distance
0.000
0.005
0.010
0.015
0.020
0.025
Leverage