Optimal Dynamic Treatment Regimes

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Summary. A dynamic treatment regime is a list of decision rules, one per time interval, for how the level of treatment will be tailored through time to an individual's changing status. The goal of this paper is to use experimental or observational data to estimate decision regimes that result in a maximal mean response. To explicate our objective and state assumptions, we use the potential outcomes model. The proposed method makes smooth, parametric assumptions only on quantities directly relevant to the goal of estimating the optimal rules. We illustrate the proposed methodology via a small simulation.

Key words: Adaptive strategies, sequential decisions, dynamic programming, causal inference

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1) Introduction

Dynamic treatment regimes are individually tailored treatments that are designed to provide treatment to individuals only when and if they need the treatment. In contrast to classical treatments in which all individuals are assigned the same level and type of treatment, dynamic treatments explicitly incorporate the heterogeneity in need for treatment across individuals and the heterogeneity in need for treatment across time within an individual. In a dynamic treatment regime, decision rules for how the dosage level and type should vary with time are specified prior to the beginning of treatment; these rules are based on time varying measurements of subject-specific need. The set of decision rules comprise the treatment regime.

Dynamic treatment regimes are also called adaptive strategies (Lavori and Dawson, 2000) or adaptive interventions (Collins, et al., 2001). When the treatment is the provision of health information designed to induce improvement in health related behaviors, dynamic regimes are called tailored communications (Kreuter and Strecher, 1996; Kreuter, et al., 2000). Dynamic treatment regimes are attractive to public policy makers because they treat only subjects who show need for treatment, freeing public and private funds for more intensive treatment of the needy. They hold the promise of reducing subject noncompliance due to over- or under- treatment (Lavori and Dawson, 2000; Collins, et al., 2001). These regimes are intended to reduce negative side-effects due to over-treatment (Bierman, et al., 2001). Dynamic regimes are used in tailoring health information content so as to provide only personally relevant information with the idea that this information will be attended to, thoughtfully processed and thus efficacious (Kreuter, Strecher and Glassman, 1999).

The goal of this paper is to provide a method for estimating optimal decision rules; rules that when implemented over a time period will produce the

highest mean response at the end of the time period. The proposed methodology will use experimental or observational longitudinal data to construct estimators of the optimal decision rules. Estimating the effects of dynamic treatment regimes has been studied at some length by Robins and colleagues (Robins, 1986, 1989, 1993, 1997; Murphy et al., 2001; van der Laan et al, 2001).

This work is motivated by the Fast Track prevention program. This is an ongoing randomized trial of a complex preventive intervention versus control. The intervention was designed to prevent the emergence of and reduce the level of conduct disorders and drug use in children considered at risk due to elevated behavior problems in kindergarten (Bierman et al., 1996; CPPRG, 1999ab; McMahon et al., 1996). Part of the intervention involved the implementation of a dynamic treatment regime designed to improve family functioning. The Fast Track team did not want to provide the highest level of home visiting to all families. It was thought that providing too many home visits might be detrimental, increasing risk for family dependency, pejorative labeling (by self and others) and cause attrition. They decided to implement a dynamic treatment as follows. At the end of each semester, beginning with the spring semester of first grade, the family counselor filled out a 6 item questionnaire composed of questions concerning the quality of parenting and family functioning. The sum is the family functioning status. The rule for assigning the number of home visits in the following semester is:

$$d_j(S_j) = 16I\{S_j \leq 8\} + 8I\{9 \leq S_j \leq 16\} + 4I\{17 \leq S_j\},\ j = 1, 2, 3, 4$$

where S_j is the family functioning status taken at the beginning of the jth semester, with low values indicating greater need. When this pioneering study was designed there was very little guidance in terms of how one might formulate the decision rule(s). Collins, Murphy and Bierman, (2001) seek to

provide qualitative guidance; the goal of this paper is provide quantitative guidance by exploring methods for estimating good rules.

The ascertainment of optimal dynamic treatment regimes belongs to the class of sequential or multistage decision problems. We consider dynamic treatment regimes in which decisions are to be made at set times; in this case the regime is a set of decision rules, with one rule per time interval. For each time interval j in $\{1, 2, ..., K\}$, denote the to-be-made treatment decision by a_j and denote the status (possibly a vector) at the beginning of time interval j by S_j. In general S contains predictors of the response. The jth decision rule will use the information available at time j and output the treatment decision, a_j. In a redesign of the Fasttrack study one might want to consider a wide variety of information as part of S including information resulting from the detailed summer interviews by outside staff, and severity in other domains such as academic and social skill development, etc. The response at the end of time interval K is denoted by Y. So the order of occurrence is S_1, a_1, S_2, ..., a_K, Y. In general we use a bar over a variable to denote that variable and all past values of the same variable, so $\bar{a}_j = (a_1, ..., a_j)$.

In many applications an expert provides the multivariate distribution of $(\bar{S}_K, Y)$ indexed by the decisions, a_1, ..., a_K. In this case, one traditionally uses backward induction (dynamic programming) to find decision rules resulting in a maximal mean response. These arguments are usually expressed as follows (Bather, 2000; Jordan and Bishop, 2001). Set

$$J_0(\bar{S}_K, \bar{a}_{K-1}) = \sup_{a_K} E\left[Y|\bar{S}_K, \bar{a}_{K-1}, a_K\right]$$

$$d_K^*(\bar{S}_K, \bar{a}_{K-1}) = \arg\sup_{a_K} E\left[Y|\bar{S}_K, \bar{a}_{K-1}, a_K\right]$$

and then for each j:

$$J_{K-j}(\bar{S}_j, \bar{a}_{j-1}) = \sup_{a_j} E\left[J_{K-j-1}(\bar{S}_{j+1}, \bar{a}_j)|\bar{S}_j, \bar{a}_{j-1}, a_j\right] \quad (1)$$

$$d_j^*(\bar{S}_j, \bar{a}_{j-1}) = \arg\sup_{a_j} E\left[J_{K-j-1}(\bar{S}_{j+1}, \bar{a}_j)|\bar{S}_j, \bar{a}_{j-1}, a_j\right]$$

The optimal rules are $d_1^*, \ldots, d_K^*$. It is important to recognize that the placement of $\bar{a}_{j-1}$ and a_j to the right of the $|$ sign is to indicate that these conditional expectations are taken with respect to the multivariate distribution of $(S_1,\ S_2,\ \ldots, S_K,\ Y)$ *indexed* by the decisions, $\bar{a}_j$; $\bar{a}_j$ plays a role similar to parameters. For example, $E\left[Y|\bar{S}_K, \bar{a}_{K-1}, a_K\right]$ is the conditional mean of Y given $\bar{S}_K$ indexed by the sequence of the decisions $\bar{a}_K$; it is not the conditional mean of Y given $\bar{S}_K$ and "other random variables," $\bar{a}_K$. The equation in (1) is a finite time version of Bellman's equation (Bellman, 1957). The function, J_{K-j} is usually called the "optimal cost-to-go" from the present state $(\bar{S}_j, \bar{a}_{j-1})$ over the future intervals of time (Bertsekas & Tsitsiklis, 1996); we call J_{K-j} the "optimal benefit-to-go" as we wish to maximize the mean response rather than minimize the mean cost. Cowell, Dawid, Lauritzen and Spiegelhalter (1999) describe the backward induction algorithm and also provide an alternate viewpoint using decision potentials.

For $K = 2$ the above is use of backwards induction to find:

$$(d_1^*, d_2^*) = \arg\sup_{d_1, d_2} E\left[E\left[E\left[Y|\bar{S}_2, a_1, a_2 = d_2(\bar{S}_2, a_1)\right]|S_1, a_1 = d_1(S_1)\right]\right]. \quad (2)$$

The formula for $K > 2$ is similar but long; see Cowell et al. (ch. 8, 1999). Statisticians who are unfamiliar with dynamic programming may find the above objective function obtuse; in the next section we use Rubin's causal model to provide an alternate form for the objective function.

Bather (2000) gives a nice introduction to and discussion of these types of problems (i.e., the multivariate distribution of $(\bar{S}_K, Y)$ indexed by the decisions, $\bar{a}_K$ is known or can be sampled). Although the steps in the dynamic programming algorithm are easily described, they are computationally complex due to the alternating steps of maximizing and averaging (Bertsekas &

Tsitsiklis, pg. 3, 1996). These problems are of great interest in the engineering literature, where the decision rules are called feedback control policies (Bertsekas & Tsitsiklis, 1996). The wide applicability of dynamic programming in finding optimal decisions combined with the computational difficulties has spawned much research. Indeed the literature for this setting is vast and spans a number of disciplines including management science, reinforcement learning, medical decision making and statistics. Some recent work by statisticians in this setting includes Shachter (1986), Owens, Shachter and Neese, (1997), Cowell, Dawid, Lauritzen and Spiegelhalter (ch.8, 1999) and Lauritzen and Nilsson (2001) all of whom use operations on influence diagrams to ascertain optimal sequential decision rules. Carlin, Kadane and Gelfand (1998) and Bielza, Müller and Insua (2001), calculate optimal decision rules by using Monte Carlo methods to simulate from the known multivariate distribution.

Our goal is to propose methodology for estimating the optimal rules when the multivariate distribution of $(\bar{S}_K, Y)$ indexed by the decisions, $\bar{a}_K$ is unknown, but experimental or observational longitudinal data are available. In order to do this we proceed as follows. First the counterfactual or potential outcome framework is used to provide a specification of (2), thus providing an alternate view of the use of dynamic programming in ascertaining optimal sequential decisions. We use this framework to formulate assumptions that justify the use of dynamic programming when only experimental or observational longitudinal data is available. Next we demonstrate that if one's goal is to estimate optimal rules, then it is unnecessary to estimate the full multivariate distribution of the longitudinal data. That is, in section 3, we model this multivariate distribution with two groups of parameters that vary independently. The first group of parameters (parameters in the "regret" functions) will be estimated and used to estimate the optimal rules and the

second group of parameters (most of which are infinite dimensional) are nuisance parameters. This approach will permit us to make smoothness (i.e. parametric) assumptions on quantities that are directly relevant for estimation of the optimal rules; we avoid making smoothness assumptions on other aspects of the data distribution. In section 4 we illustrate a method that permits one to estimate the parameters in the regret functions without estimating the nuisance parameters. More importantly this method will provide a computational alternative to the interweaving maximization and averaging steps of the dynamic programming algorithm The last section provides simulation results that illustrate the proposed method.

2) Potential Outcomes and Dynamic Programming

Neyman (1923) introduced potential outcomes to analyze the causal effect of time-independent treatments in randomized studies. Rubin (1978) explicated Neyman's ideas and extended Neyman's work to the analysis of causal effects of time-independent treatments from observational data. Robins (1986, 1987) proposed a formal theory of causal inference that extended both Neyman's and Rubin's work to assess the direct and indirect effects of time varying treatments from experimental and observational longitudinal studies. We use these works to specify our objective and to state the assumptions.

In the following we define the potential outcomes; these potential outcomes will be related to the observable data later. We use upper case Roman letters to denote random variables and lower case Roman letters to denote nonrandom variables. Since in dynamic treatment regimes we only manipulate or assign treatments, the potential outcomes are indexed only by treatments. Furthermore, we assume that a subject's outcomes are not

influenced by other subjects' treatments so we index each subject's potential outcomes by only his/her treatments (see Cox, 1958; Rubin, 1986 for a more complete discussion). Thus corresponding to each fixed value of the treatment vector, $\bar{a}_K$ we conceptualize a potential response denoted by $Y(\bar{a}_K)$ where $Y(\bar{a}_K)$ is the response at the end of the Kth interval that a subject would have if he/she followed the treatments, $\bar{a}_K$. Let $\mathcal{A}_K$ be the collection of all possible K-vectors of treatments decisions. The set of all potential responses is $\{Y(\bar{a}_K) : \bar{a}_K \text{ varying in } \mathcal{A}_K\}$. The status at the beginning of time interval j is an intermediate outcome of (past) treatments and thus the set of intermediate outcomes at time j is $\{S_j(\bar{a}_{j-1}) : \bar{a}_{j-1}$ varying in the first $j-1$ components of $\mathcal{A}_K\}$. Denote all of the subject's potential outcomes by $O_{sr} = \{S_2(a_1), ..., S_{K-1}(\bar{a}_{K-2}), Y(\bar{a}_K); \bar{a}_K \in \mathcal{A}_K\}$.

The potential outcomes model sheds light on the function to be maximized in (2) as follows. The mean response for regime $d_1, \ldots, d_K$ is

$$E[Y(\bar{d}_K)] = E\Big[Y(\bar{a}_K)_{a_1=d_1(S_1),\ldots,a_K=d_K(\bar{S}_K(\bar{a}_{K-1}),\bar{a}_{K-1})}\Big] \tag{3}$$

where a bar over a variable is used to denote that variable and all past values of the same variable (e.g. $\bar{a}_K = a_1, \ldots, a_K$ and $\bar{S}_K(\bar{a}_{K-1}) = S_1, S_2(a_1), \ldots, S_K(\bar{a}_{K-1})$). The optimal rules should maximize this mean. The mean can be written as a repeated expectation, in particular for $K = 2$, we have that

$$E\Big[Y(\bar{d}_2)\Big] = E\Big[E\Big[E[Y(\bar{a}_2) \mid \bar{S}_2(a_1)]_{a_2=d_2(\bar{S}_2(a_1),a_1)}\Big|S_1\Big]_{a_1=d_1(S_1)}\Big].$$

As before we may place a_1 and a_2 to the right of the $|$ sign to indicate that these conditional expectations are indexed by the decisions. Then an alternate version is:

$$E\Big[E\Big[E[Y(\bar{a}_2)|\ \bar{S}_2(a_1), a_1, a_2 = d_2(\bar{S}_2(a_1), a_1)]\Big|S_1, a_1 = d_1(S_1)\Big]\Big]. \tag{4}$$

From the similarity between the above display and (2), we see that the dynamic programming algorithm, as expected, has the goal of finding the regime that maximizes the mean response.

Now we connect the potential outcomes with observations in a longitudinal data set and we express (4) in terms of this data. The observable data for a subject is X=$\{ S_1, A_1, S_2, \ldots, A_K, Y\}$ where $\bar{A}_K$ is the vector of stochastic treatment decisions. $\bar{A}_K$ takes values in $\mathcal{A}_K$. We make Robins' (1997) consistency assumption. That is, we assume that the potential outcomes are connected to the subject's data by the equalities, $Y = Y(\bar{A}_K)$, $S_K = S_K(\bar{A}_{K-1})$, and so on, including $S_2 = S_2(A_1)$. In the following we use either Y or $Y(\bar{A}_K)$ to denote the observed response at the end of time interval K and either S_j or $S_j(\bar{A}_j)$ to denote the observed status at the beginning of time interval j. Thus the observable data are the pretreatment information (S_1) plus the potential outcomes corresponding to the treatment pattern $\bar{A}_K$. Most of a given subject's potential outcomes are missing; only the potential outcomes corresponding to the treatment pattern $\bar{A}_K$ can be observed.

In order to express (4) in terms of the observable data we will need to make assumptions. To see why consider the following scenario. Suppose that among individuals with the same past status levels and past treatment levels, the individuals with treatment $A_K = high$ differ from the individuals with treatment $A_K = low$ and the reason for this difference is not contained in the available data. To decide if the decision, *high* treatment is optimal (i.e. better than the decision *low* treatment) we compare the average value of Y for those with $A_K = high$ with the average value of Y for those with $A_K = low$. However any apparent difference in the two conditional means may be due to the difference in composition between the individuals with treatment $A_K = high$ and the individuals with treatment $A_K = low$.

That is, A_K may not be conditionally independent of the potential outcomes, O_{sr}, conditional on $(\bar{S}_{K-1},\ \bar{A}_{K-1})$, because there may be unmeasured "confounders" that determine treatment and are associated with the potential outcomes. In general assumptions about this distributional relationship must be used to identify causal effects and thus permit causal inference (for discussion, see section 11, of Robins, 1997). We make the following independence assumption (Robins, 1997) on the relationship between the potential outcomes, O_{sr}, and the treatment decisions, $\bar{A}_K$. We assume:

No Unmeasured Confounders: *For each* $j = 1, ..., K$, A_j *is independent of* O_{sr} *given* $\{S_1,\ A_1,\ S_2,\ A_2, ...,\ S_j\}$.

This assumption is also called sequential ignorability, (Robins, 2000). An alternate statement of this assumption should be possible using the methods in Robins and Greenland (1992) or Dawid, Didelez and Murphy (2001). These methods replace potential outcomes with potential experiments.

The phrase, "no unmeasured confounders" should not be misinterpreted; perhaps a better phrase would be "no unmeasured direct confounders," as the assumption is a statement about treatment selection conditional on past information. Intuitively this means that an unmeasured confounder may only influence treatment selection through the measured past information. The no unmeasured confounders assumption would be true if the treatments are sequentially randomized. Treatments are sequentially randomized when at each time j, the treatment, A_j is randomized with randomization distribution allowed to depend on $\{S_1,\ A_1,\ S_2,\ A_2, ...,\ S_j\}$ (Robins,1997). Lavori and Dawson (2000) and Lavori, Dawson and Rush (2000) propose that researchers implement sequentially randomized experiments so as to estimate optimal decisions rules (instead of sequential randomization they use the phrase, biased adaptive within-subject randomization). An additional setting in which the no unmeasured confounders assumption would be true is in

computer experiments that are designed using a distribution for the decision, A_j, depending only on past information. Of course for a given observational data set, one may believe that the S_j's are sufficiently rich so that the no unmeasured confounders assumption holds.

Assuming no unmeasured confounders, we can write (3) which is a function of the multivariate distribution of the potential outcomes, as a function of the multivariate distribution of the longitudinal data:

$$E\Big[E\Big[\ldots E[E[Y|\bar{S}_K,\ \bar{A}_{K-1},\ A_K = d_K]$$

$$|\bar{S}_{K-1},\ \bar{A}_{K-2},\ A_{K-1} = d_{K-1}]\ldots\Big|S_1,\ A_1 = d_1\Big]\Big] \quad (5)$$

where d_j implicitly denotes $d_j(\bar{S}_j, \bar{A}_{j-1})$. This is Robins' G-computation formula (Robins, 1986, 1987, 1989, 1997 and Gill and Robins, 2001). For $K = 2$ (5) is

$$E[Y(\bar{d}_2)] = E\Big[E\Big[E[Y|\bar{S}_2, A_1, A_2 = d_2(\bar{S}_2, A_1)]\Big|S_1, A_1 = d_1(S_1)\Big]\Big]. \quad (6)$$

Note the subtle difference between the above equation and (4) and the repeated expectation in (2); (2) and (4) are functions of conditional distributions *indexed* by treatment decisions $\bar{a}_2$ whereas the above is a function of conditional distributions, *conditioning* on the treatment decisions. It may appear to be patently obvious that (6) and the repeated expectation in (2) should be equal. However from the discussion preceding the statement of the no unmeasured confounders assumption we know that this may not be true. The beauty of the no unmeasured confounders assumption combined with Robin's G-computation formula is that they provide a means by which we can say that the repeated expectation in (2) and (6) are equal. Robin's G-computation formula is the formula that provides the mean response to a dynamic regime in terms of the longitudinal data distribution.

A proof of Robin's G-computation formula is provided by lemma 2 in the appendix. This proof assumes that the range of the treatment decisions, $\bar{A}_K$ is countable ($\mathcal{A}_K$ is countable). Denote the conditional probability function for each A_j given $\bar{S}_j,\ \bar{A}_{j-1}$ by $p_j(a_j|\bar{S}_j,\ \bar{A}_{j-1})$. The proof assumes that the regime $\bar{d}_K$ satisfies

$$P\left[\prod_{j=1}^{K} p_j\Big(d_j(\bar{S}_j, \bar{A}_{j-1})|\bar{S}_j, \bar{A}_{j-1}\Big) > 0\right] = 1. \tag{7}$$

That is, to prove that the repeated expectation in (2) and (6) are equal we not only assume no unmeasured confounders, we also make the eminently sensible assumption that treatment patterns consistent with the regime $\bar{d}_K$ can occur in the longitudinal data. See Gill and Robins, (2001) for more general conditions and proof.

Denote the class of regimes (i.e. the vector of decision rules) satisfying (7) by D_P. We subscript D by the probability P since the class of regimes may vary by the distribution of the longitudinal data. For the remainder of the paper we take as our goal that of finding a regime that maximizes (5) over the class D_P. The assumption of no unmeasured confounders is only used to justify the use of (5) as an appropriate objective function for the purposes of estimating optimal regimes.

For each treatment level, a_K satisfying $p_K(a_K|\bar{S}_K, \bar{A}_{K-1}) > 0$ define,

$$Q_0(\bar{S}_K, \bar{A}_{K-1}, a_K) = E\left[Y|\bar{S}_K, \bar{A}_{K-1}, A_K = a_K\right]$$

Next define,

$$J_0(\bar{S}_K, \bar{A}_{K-1}) = \sup_{a_K : p_K(a_K|\bar{S}_K, \bar{A}_{K-1}) > 0} Q_0(\bar{S}_K, \bar{A}_{K-1}, a_K).$$

For each $j = 0, \ldots, K-1$ and a_j satisfying $p_j(a_j|\bar{S}_j, \bar{A}_{j-1}) > 0$ iteratively define,

$$Q_{K-j}(\bar{S}_j, \bar{A}_{j-1}, a_j) = E\left[J_{K-j-1}(\bar{S}_{j+1}, \bar{A}_j)|\bar{S}_j, \bar{A}_{j-1}, A_j = a_j\right]$$

and

$$J_{K-j}(\bar{S}_j, \bar{A}_{j-1}) = \sup_{a_j : p_j(a_j|\bar{S}_j, \bar{A}_{j-1})>0} Q_{K-j}(\bar{S}_j, \bar{A}_{j-1}, a_j). \tag{8}$$

We call the functions $J_0, \ldots J_{K-1}$, the optimal benefit-to-go functions. Note that these functions differ from the displays in (1) in two ways, first the above optimal benefit-to-go functions are conditional on treatment decisions whereas in (1), they are indexed by treatment decisions and second we maximize over a restricted set of decision rules since we are unable to evaluate treatment decisions that can not occur in the longitudinal data.

Beginning with J_0 and then ascertaining each optimal benefit-to-go function forms the steps of a dynamic programming argument that ends with the maximal value equal to $J_{K-1}(S_1)$. This process is equivalent to maximizing (5) over the class D_P. Indeed we have,

Theorem 1: Assume that $\mathcal{A}_K$ is countable. Assume $E\Big[|Y|\Big|\bar{S}_K,\ \bar{A}_K\Big]$ is bounded $a.s.$ Then,

$$\sup_{\bar{d}_K \in D_P} E\Big[E\Big[\ldots E[E[Y|\bar{S}_K,\ \bar{A}_{K-1},\ A_K = d_K]$$

$$|\bar{S}_{K-1},\ \bar{A}_{K-2},\ A_{K-1} = d_{K-1}]\ldots\Big|S_1,\ A_1 = d_1\Big]\Big] \tag{9}$$

is equal to $E[J_{K-1}(S_1)]$.
The proof is in the appendix.

If we assume that the supremum is achieved at a $\bar{d}_K^*$ in D_P (e.g. this would occur if the number of possible treatments is finite), then we can write the optimal benefit-to-go functions in terms of the potential outcomes for Y. In this case

$$J_{K-j}(\bar{S}_j, \bar{A}_{j-1}) = E[Y(\bar{A}_{j-1}, d_j^*, \ldots, d_K^*)|\bar{S}_j, \bar{A}_{j-1}] \tag{10}$$

for each $j = 1, \ldots, K$. This can be derived by following the same steps as in the proof of Theorem 1 (see the appendix). Thus the optimal benefit-to-go function represents the mean potential response conditional on the past and assuming that optimal decisions will be followed in the future.

3) The Regret Functions

Our goal is to estimate an optimal regime (i.e., a regime that maximizes (5) over the class D_P). An initial approach is to model the multivariate distribution of $(\bar{S}_K,\ \bar{A}_K,\ Y)$, say using a parametric, semiparametric or nonparametric model, and then apply the dynamic programming argument. By careful choice of a semiparametric model we are able to avoid the dynamic programming step. Instead of parameterizing conditional mean functions or conditional distribution functions we parametrize and then estimate "regret functions." At the end of this section we provide the semiparametric model induced by parametrization of the regrets.

The regret functions are defined for each $j = 1, \ldots, K$ as,

$$\mu_j(\bar{S}_j, \bar{A}_{j-1}, a_j) = J_{K-j}(\bar{S}_j, \bar{A}_{j-1}) - Q_{K-j}(\bar{S}_j, \bar{A}_{j-1}, a_j).$$

Note that the μ's satisfy the constraint,

$$\inf_{a_j : p_j(a_j|\bar{S}_j, \bar{A}_{j-1}) > 0} \mu_j(\bar{S}_j, \bar{A}_{j-1}, a_j) = 0.$$

The regret function $\mu_j(\bar{S}_j, \bar{A}_{j-1}, a_j)$, provides the increase in the benefit-to-go we forgo by making decision a_j rather than the optimal decision at time j. That is, the predictor effect is measured in terms of changes from the optimal predictor value. This is most clearly seen when the supremum in (9)

is achieved at a $\bar{d}_K^* \in D_P$, in which case the regret is given by (using the potential outcomes model)

$$\mu_j(\bar{S}_j, \bar{A}_{j-1}, a_j) = E[Y(\bar{A}_{j-1}, d_j^*, \ldots, d_K^*)|\bar{S}_j, \bar{A}_{j-1}] \; - \\ E[Y(\bar{A}_{j-1}, a_j, d_{j+1}^*, \ldots, d_K^*)|\bar{S}_j, \bar{A}_{j-1}].$$

It is clear that the backwards induction argument can be based on minimizing the regrets instead of maximizing the Q functions. Thus if we had estimates of the regrets we could then derive estimates of the optimal rules.

We directly model the regrets; this model may be nonparametric, semiparametric or parametric. Estimation is discussed in the next section. One possible class of parametric models is based on a known "link" function $f(u)$; these functions provide the link between the regret and the decision rule. The minimal value of each f should be achieved at $u = 0$ and be equal to 0 ($f(0) = 0$); so each f is a nonnegative function. For a positive scale parameter, $\eta_j(\bar{s}_j, \bar{a}_{j-1})$ set

$$\mu_j(\bar{s}_j, \bar{a}_j) = \eta_j(\bar{s}_j, \bar{a}_{j-1}) f\Big(a_j - d_j(\bar{s}_j, \bar{a}_{j-1})\Big). \tag{11}$$

Note that the constraints on the link function imply that $d_j(\bar{s}_j, \bar{a}_{j-1})$ is the optimal decision rule based on past information $(\bar{s}_j, \bar{a}_{j-1})$. We form parsimonious parametric models for the optimal decision $d_j(\bar{s}_j, \bar{a}_{j-1})$ and for the scale parameter $\eta_j(\bar{s}_j, \bar{a}_{j-1})$. Parsimony can be important; in many settings a simple rule is easier to implement than a complicated rule.

The shape of the link, f determines how the modeled regret will change as a treatment decision deviates from the optimal. To provide flexibility in the rate at which the modeled regret changes as a treatment decision deviates from the optimal, we model and estimate a multiplicative unknown scale parameter, $\eta_j(\bar{s}_j, \bar{a}_{j-1})$. Large values of $\eta_j(\bar{s}_j, \bar{a}_{j-1})$ imply that a small

difference in the treatment decision from the optimal produces a large regret and vice versa. Suppose the possible decisions are real values (e.g. dose of a drug), then one might believe that the regret will have an "U" shape so that for doses smaller than the optimal, the subject receives insufficient treatment, yet for doses larger than the optimal the subject suffers toxicity or side effects and thus the subject does not benefit as much as would be the case if the optimal dose is delivered. In this case we might use $f(u) = u^2$. Alternately we might believe the particular treatment does not cause toxicity or side effects; in this case the link might be positive quadratic for $u < 0$ and equal to zero thereafter. In the future it will be important to model the link rather than assume it known.

In order to provide a more flexible regret we can combine two links; for example we might base a model for the regret on, $\mu_j(\bar{s}_j, \bar{a}_j) = \eta_j(\bar{s}_j, \bar{a}_{j-1}) f\Big(a_j - d_j(\bar{s}_j, \bar{a}_{j-1})\Big) + \eta'_j(\bar{s}_j, \bar{a}_{j-1}) f'\Big(a_j - d_j(\bar{s}_j, \bar{a}_{j-1})\Big)$ where $f(u) = u^2 I\{u \leq 0\}$ and $f'(u) = u^2 I\{u \geq 0\}$. We can allow the link function to change by interval and/or by past information. This is particularly relevant if the type of decision may change by interval and/or if the type of decision differs by most recent status and most recent past decision.

If in an interval two different decisions must be made, then we may make the decisions sequentially forming two "intervals" from the one and using a different link for each decision type. For example suppose in each interval educational staff have to make two decisions, first the staff member must decide if the child is to receive special education or not. If the child is to receive special education then the staff member must recommend a certain number of minutes of special education per day; otherwise the staff member must recommend a number of tutoring sessions per week. First we break each interval into two intervals corresponding to the two decisions, then we might use (11) for a given link f and $a_j \in \{0, 1\}$ denoting special education

by 1 and no special education by 0. Then for possibly different link functions, f' and f'' the regret for the second decision would be

$$\mu_{j+1}(\bar{s}_{j+1}, \bar{a}_{j+1}) = I\{a_j = 1\}\eta_{j+1}(\bar{s}_{j+1}, \bar{a}_j) f'\Big(a_{j+1} - d_{j+1}(\bar{s}_{j+1}, \bar{a}_j)\Big)$$
$$+ I\{a_j = 0\}\eta_{j+1}(\bar{s}_{j+1}, \bar{a}_j) f''\Big(a_{j+1} - d_{j+1}(\bar{s}_{j+1}, \bar{a}_j)\Big)$$

where the link f' is used to parameterize the regret when one is choosing among minutes of special education and the link f'' is used to parameterize the regret when one is deciding the frequency of tutoring sessions. In the next section we provide a method to estimate the regret functions.

We can write the mean of Y given $(\bar{S}_K,\ \bar{A}_K)$ in terms of the regrets,

$$E[Y|\bar{S}_K, \bar{A}_K] = \mu_0 + \sum_{j=1}^{K} \phi_j(\bar{S}_j, \bar{A}_{j-1}) - \sum_{j=1}^{K} \mu_j(\bar{S}_j, \bar{A}_j) \tag{12}$$

where $\mu_0 = EJ_{K-1}(S_1)$, and the ϕ_j's are defined so that the right hand side is equal to the left hand side; $\phi_j(\bar{S}_j, \bar{A}_{j-1}) = J_{K-j}(\bar{S}_j, \bar{A}_{j-1}) - Q_{K-j+1}(\bar{S}_{j-1}, \bar{A}_{j-1})$ for $j = 1, \ldots, K$. Note that $E[\phi_j(\bar{S}_j, \bar{A}_{j-1})|\bar{S}_{j-1}, \bar{A}_{j-1}]$ is zero. As mentioned previously, parametrization of the regrets induces a semiparametric model for the longitudinal data, X. When Y is continuous this model is given by,

$$g\left(y - \mu_0 - \sum_{j=1}^{K} \left(\phi_j(\bar{s}_j, \bar{a}_{j-1}) - \mu_j(\bar{s}_j, \bar{a}_j)\right) \Big| \bar{s}_K, \bar{a}_K\right) \times$$
$$\prod_{j=1}^{K} p_j(a_j|\bar{s}_j, \bar{a}_{j-1}) \prod_{j=1}^{K} f_j(s_j|\bar{s}_{j-1}, \bar{a}_{j-1})$$

where

- $g(\cdot|\bar{s}_K, \bar{a}_K)$ is the mean zero conditional density of Y given $(\bar{S}_K, \bar{A}_K)$ and must belong to the class of mean zero densities for fixed values of $(\bar{s}_K, \bar{a}_K)$,

- $p_j(a|\bar{s}_j, \bar{a}_{j-1})$ denotes the conditional probability function for each A_j given $(\bar{S}_j,\ \bar{A}_{j-1})$ at times $j = 1, \ldots, K$ and each p_j must belong to the class of probability functions in a for fixed values of $(\bar{s}_j, \bar{a}_{j-1})$,

- $f_j(s|\bar{s}_{j-1}, \bar{a}_{j-1})$ is the conditional density of S_j given $(\bar{S}_{j-1},\ \bar{A}_{j-1})$ at times $j = 1, \ldots, K$, each f_j must belong to the class of probability densities in s for fixed values of $(\bar{s}_{j-1}, \bar{a}_{j-1})$.

- $\mu_j(\bar{s}_j, \bar{a}_j)$ is the jth regret, $J_{K-j}(\bar{s}_j, \bar{a}_{j-1}) - Q_{K-j}(\bar{s}_j, \bar{a}_j)$ and each μ_j must belong to the class of functions satisfying $\inf_{a_j : p_j(a_j|\bar{s}_j, \bar{a}_{j-1})>0} \mu_j(\bar{s}_j, \bar{a}_j) = 0$,

- $\phi_j(\bar{s}_j, \bar{a}_{j-1})$ is $J_{K-j}(\bar{s}_j, \bar{a}_{j-1}) - Q_{K-j+1}(\bar{s}_j, \bar{a}_{j-1})$ and must belong to the class of functions satisfying $\int \phi_j(\bar{s}_j, \bar{a}_{j-1}) f_j(s_j|\bar{s}_{j-1}, \bar{a}_{j-1})\, ds_j = 0$,

- μ_0 is $EJ_{K-1}(S_1)$ and takes values on the real line. μ_0 is the mean response to the optimal decision regime.

As discussed above we are primarily interested in the parameters composing the regrets, μ_j; the unknown functions g, p_j's, f_j's, ϕ_j's and scalar, μ_0 are nuisance parameters.

Advantages of Modeling the Regrets:

Modeling the regrets has several nice conceptual and practical properties. First, we parameterize the optimal rules; that is, we impose parsimony on aspects of the multivariate distribution of $(\bar{S}_K,\ \bar{A}_K,\ Y)$ that are of direct relevance for our goal. In particular, this approach combined with the estimation method to follow, permits the straightforward use of statistical methods such as hypothesis testing and model selection. Thus we are able to test if particular features of the past information are needed in the optimal rule.

A second nice property is that the constraints on the form of the optimal decision are made explicit. To highlight this second property we contrast the direct parametric modeling of the regrets with parameterizing both $Q_0(\bar{S}_K, \bar{a}_K) = E[Y|\bar{S}_K, \bar{A}_K = \bar{a}_K]$ and the density of S_j given $(\bar{S}_{j-1}, \bar{A}_{j-1})$ for each j and then by alternating supremum and averaging steps forming estimates of all of the Q functions. This alternate approach leads to implicit constraints on the form of the regret functions, $\mu_1, \ldots, \mu_{K-1}$ and the $Q_1, \ldots, Q_{K-1}$ functions. Implicit constraints on $Q_1, \ldots, Q_{K-1}$ occur because these are joint functions of Q_0 and the conditional distributions of the S_j's.

The finite dimensional parametric models for Q_0 and the distribution of S_j given $(\bar{S}_{j-1}, \bar{A}_{j-1})$ also constrain the form of the regret as follows. According to the dynamic programming algorithm we would first maximize Q_0 over a_K yielding $J_0(\bar{S}_K, \bar{a}_{K-1})$. Thus the parameterization of Q_0 determines the form of J_0. From (12) we have that $J_0(\bar{S}_K, \bar{a}_{K-1}) = \mu_0 + \sum_{j=1}^{K} \phi_j(\bar{S}_j, \bar{a}_{j-1}) - \sum_{j=1}^{K-1} \mu_j(\bar{S}_j, \bar{a}_j)$ (recall $Q_0 = E[Y|\bar{S}_K, \bar{A}_K = \bar{a}_K]$). Thus the parameterization of Q_0 determines the shape of this function, particularly in a_{K-1} via the $\phi_K(\bar{S}_K, \bar{a}_{K-1}) - \mu_{K-1}(\bar{S}_{K-1}, \bar{a}_{K-1})$ term. At the same time, the parametric model for the distribution of S_K given $(\bar{S}_{K-1}, \bar{A}_{K-1})$ constrains the shape of $\phi_K(\bar{s}_K, \bar{a}_{K-1})$ in a_{K-1} since $E[\phi_K(\bar{S}_K, \bar{A}_{K-1})|\bar{S}_{K-1}, \bar{A}_{K-1})] = 0$. These two constraints lead to a limited set of forms for the regret function. This is particularly a problem when the parametric models are nonlinear. This situation is similar to that highlighted by Robins and Wasserman (1997) who in testing for effects of treatment decisions, found that the hypothesis of no treatment effect may be excluded by the explicit restrictions imposed by parametric models on other, less scientifically interesting, parts of the multivariate data distribution. Because the constraints are implicit it is difficult in any given situation to check how much and in what way they constrain the regret function.

An additional nice property resulting from direct models for the regrets is that parameterization of the regrets does not place constraints on other aspects of the multivariate distribution of $(\bar{S}_K,\ \bar{A}_K,\ Y)$ when $E[Y|\bar{S}_K, \bar{A}_K]$ is unbounded. For continuous Y with unbounded support, this can be seen from the likelihood provided earlier. Since Y has unbounded support there is no a priori restriction on the value of $E[Y|\bar{S}_K, \bar{A}_K]$. Thus as can be seen from the likelihood, μ_j and p_j are variation independent of the nuisance parameters μ_0, g and ϕ_j, f_j, for $j = 1, \ldots, K$. We are interested in parameters composing μ_j and will use models for p_j; parametric models for the μ_j's and p_j's do not constrain the possible values of the nuisance parameters and all modeling assumptions are explicit. That is, we know that we are not accidently making implicit, perhaps untenable, assumptions about nuisance parts of the multivariate distribution. To highlight this property consider an alternate approach of directly parameterizing each of the Q functions. Note that

$$Q_1(\bar{S}_{K-1}, \bar{a}_{K-1}) = E[inf_{a_K} Q_0(\bar{S}_K, \bar{a}_K)|\bar{S}_{K-1}, \bar{A}_{K-1} = \bar{a}_{K-1}].$$

Thus parametric models for Q_1 and Q_0 constrain the conditional distribution of S_K given $(\bar{S}_{K-1}, \bar{A}_{K-1})$. This is a well known problem regarding the compatibility of marginal and conditional models (Q_0 plays the role of the conditional mean and Q_1 plays the role of the marginal mean). For a now classic example, see Hougaard (1986) who shows that if one assumes that the proportional hazards model from survival analysis holds for both marginal and conditional models, then subject to natural conditions, the mixing density (here the density of S_K given $(\bar{S}_{K-1}, \bar{A}_{K-1})$) must be a positive stable distribution with infinite mean. Thus the restrictions on the conditional distribution of S_K given $(\bar{S}_{K-1}, \bar{A}_{K-1})$ can be quite surprising.

Bertsekas and Tsitsiklis (1996) working in a similar setting to the introduction (i.e. the distribution of $\bar{S}_K, Y$, indexed by the treatment decisions is known or can be simulated from) illustrate the approximation of the Q functions by neural network architectures such as splines, wavelets and classical neural networks. Brockwell and Kadane (2001) use a discretization method combined with the use of "features" summarizing the past history to approximate the Q functions. These approaches share the first property with the method proposed here, that is, they impose parsimony on aspects of the multivariate distribution of $(\bar{S}_K,\ \bar{A}_K,\ Y)$ that are of direct relevance for the goal of estimating an optimal regime. The architectures discussed by Bertsekas and Tsitsiklis can be considered nonparametric modeling methods when S can only assume a few values and the possible decisions are small; in this case this method shares the third property of avoiding implicit constraints on other aspects of the multivariate distribution. However, in many cases S may assume many values or the set of possible decisions is not small; then due to the curse of dimensionality this approach must be considered parametric and thus implicit restrictions are placed on the conditional density of each S_j given $\bar{S}_{j-1}$.

A fourth nice property of this modeling approach is that it directly leads to a simple estimator of the mean response to the optimal dynamic regime. This follows from (12) which implies,

$$E[J_{K-1}(S_1)] = \sum_{j=1}^{K} E[\mu_j(\bar{S}_j, \bar{A}_j)] + E[Y].$$

Under the assumption of no unmeasured confounders, $E[J_{K-1}(S_1)]$ is the mean response to an optimal dynamic regime. Thus given estimators of the regrets and a sample, $(\bar{S}_{Ki},\ \bar{A}_{Ki},\ Y_i,\ i = 1, \ldots, n)$, an estimator of the mean response to an optimal dynamic regime is,

$$n^{-1} \sum_{i=1}^{n} \left(\sum_{j=1}^{K} \widehat{\mu}_j(\bar{S}_{ji}, \bar{A}_{ji}) + Y_i \right).$$

All four properties are analogs of properties Robins (1986,1987,1989, 1997) established for structural nested mean models. Structural nested mean models are models for effects relative to the predictor value of 0, whereas the models presented here are for effects relative to the optimal predictor value. Additionally, the likelihood here is similar in form to the likelihood for Robins' structural nested mean models.

3) Estimation

Estimation procedures can be based on the following least squares characterization of the regret functions. Denote the true regret functions with a subscript of 0, i.e., $\mu_{01}, \ldots, \mu_{0K}$. Also we assume that the support of each conditional probability function $p_j(a|\bar{s}_j, \bar{a}_{j-1})$ for given $(\bar{s}_j, \bar{a}_{j-1})$ is known. Thus the infimum in the definition of the regret function is over a known set of decisions.

Theorem 2: Assume that both Y and each component of $\bar{\mu}_{0K}$ is square integrable. Then given a vector of square integrable functions $\bar{\mu}_K$, where each μ_j satisfies both $\inf_{a:p_j(a|\bar{S}_j,\bar{A}_{j-1})>0} \mu_j(\bar{S}_j, \bar{A}_{j-1}, a) = 0$ and

$$E\left[Y + \sum_{l=1}^{K} \mu_l(\bar{S}_l, \bar{A}_l) - \sum_a \mu_j(\bar{S}_j, \bar{A}_{j-1}, a) p_j(a|\bar{S}_j, \bar{A}_{j-1})\right]^2 \leq$$

$$E\left[Y + \sum_{l=1, l\neq j}^{K} \mu_l(\bar{S}_l, \bar{A}_l) + m_j(\bar{S}_j, \bar{A}_j) - \sum_a m_j(\bar{S}_j, \bar{A}_{j-1}, a) p_j(a|\bar{S}_j, \bar{A}_{j-1})\right]^2 \quad (13)$$

for all square integrable m_j, $j = 1, \ldots, K$ we have that $\bar{\mu}_K$ is $a.s.$ equal to $\bar{\mu}_{0K}$. We can replace Y by $Y + c$ for a scalar c and/or we can replace the $\sum_{l=1}^{K}$ by $\sum_{l\geq j}^{K}$ and the sum $\sum_{l=1,l\neq j}^{K}$ by $\sum_{l>j}^{K}$ and in both cases the same result holds. See the appendix for a proof of this result.

There are a variety of ways to base estimation of the regret functions on the above least squares characterization. For simplicity suppose the conditional probability functions, $\bar{p}_K$ are known. First we formulate a model for the regrets with a p-dimensional unknown parameter, β, say $\mu_j(\bar{s}_j, \bar{a}_j; \beta)$ so that $\inf_a \mu_j(\bar{s}_j, \bar{a}_{j-1}, a; \beta) = 0$. Then we replace the expectation in (13) by an average over the data with the aim of finding a $\widehat{\beta}$ for which

$$\mathbb{P}_n \left[Y + \sum_{l=1}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \widehat{\beta}) - \sum_a \mu_j(\bar{S}_j, \bar{A}_{j-1}, a; \widehat{\beta}) p_j(a|\bar{S}_j, \bar{A}_{j-1}) \right]^2 \leq$$

$$\mathbb{P}_n \left[Y + \sum_{l=1, l\neq j}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \widehat{\beta}) + m_j(\bar{S}_j, \bar{A}_j) - \sum_a m_j(\bar{S}_j, \bar{A}_{j-1}, a) p_j(a|\bar{S}_j, \bar{A}_{j-1}) \right]^2$$

for chosen m_j, $j = 1, \ldots, K$ (for a function f of the ith subject's data, X_i, $\mathbb{P}_n f(X)$ is defined as $1/n \sum_{i=1}^{n} f(X_i)$, assuming that the sample observations are independent draws from a distribution). In the simulations, we use the model for the regrets as the m_j.

In general the conditional probability functions $(\bar{p}_K)$ for the longitudinal data will be unknown (however we continue to assume that the support of each conditional probability function $p_j(a|\bar{s}_j, \bar{a}_{j-1})$ for given $(\bar{s}_j, \bar{a}_{j-1})$ is known). These densities can be estimated by postulating a model and then using maximum likelihood, i.e., given the model $p_j(a|\bar{s}_j, \bar{a}_{j-1}; \alpha)$, $j = 1, \ldots, K$ with unknown parameter α, maximize the log-likelihood

$$\mathbb{P}_n \left[\sum_{j=1}^{K} \log p_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \alpha) \right]$$

to find $\widehat{\alpha}_n$. In this paper we assume that the support of each p_j does not vary by the unknown parameter α. To estimate the parameters in the regret functions, we search for a $(\widehat{\beta}_n, \widehat{c}_n)$ for which,

$$\sum_{j=1}^{K} \mathbb{P}_n \left[Y + \widehat{c}_n + \sum_{l=1}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \widehat{\beta}_n) - \sum_a \mu_j(\bar{S}_j, \bar{A}_{j-1}, a; \widehat{\beta}_n) p_j(a|\bar{S}_j, \bar{A}_{j-1}; \widehat{\alpha}_n) \right]^2 \leq$$

$$\sum_{j=1}^{K} \mathbb{P}_n \Big[Y + c + \sum_{l=1, l\neq j}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \widehat{\beta}_n) + \mu_j(\bar{S}_j, \bar{A}_j; \beta)$$

$$- \sum_a \mu_j(\bar{S}_j, \bar{A}_{j-1}, a; \beta) p_j(a|\bar{S}_j, \bar{A}_{j-1}; \widehat{\alpha}_n) \Big]^2 \quad (14)$$

for all β, c. (The inclusion of the unknown scalar, c, does not change consistency but greatly improves the stability of the algorithm.) One way to computationally implement the search is to start with an initial value of $\widehat{\beta}_n$ say $\widehat{\beta}_{n1}$, substitute $\widehat{\beta}_{n1}$ for $\widehat{\beta}_n$ in (14), minimize over (β, c), to get $(\widehat{\beta}_{n2}, \widehat{c})$, discard $\widehat{c}$, replace $\widehat{\beta}_n$ in (14) with $\widehat{\beta}_{n2}$ and iterate the minimization process until convergence. The least squares criterion uses the conditional variability of the decision levels in the data in order to estimate the optimal decisions. Intuitively this can be seen by acting as if the above least squares function (14) is smooth in β and differentiating with respect to β and c. The A_j's minus their conditional expectations given the past, play an analogous role to covariates in a linear regression. This means, quite naturally, that if given the past information A_j is deterministic, this method can not lead to estimators of the decision rules.

When the modeled regrets and optimal decisions are smooth functions of β, simple Taylor series arguments can be used to derive an estimator of the asymptotic variance of $\widehat{\beta}_n$. The formula is provided in the appendix. An estimator of the mean response (μ_0) to an optimal dynamic regime is

$$\widehat{\mu}_0 = \mathbb{P}_n \left[\sum_{j=1}^{K} \mu_j(\bar{S}_j, \bar{A}_j; \widehat{\beta}) + Y \right].$$

The formula for the asymptotic variance $\widehat{\mu}_0$ is also in the appendix.

Further Comments:

(1) The least squares characterization in (13) and/or (14) leads to relatively simple computations in contrast with the very natural approach of

first, estimating $Q_0(\bar{S}_K, \bar{a}_K) = E[Y|\bar{S}_K, \bar{A}_K = \bar{a}_K]$ and the density of S_j given $(\bar{S}_{j-1}, \bar{A}_{j-1})$ for each j and second, carrying out the interwoven supremum and expectation steps composing the dynamic programming algorithm. See Bertsekas and Tsitsiklis (pg. 3, 1996) for comments on the computational issues. Furthermore as discussed at the end of section 2, in order to avoid imposing implicit constraints on the decision rule, one would want to make the models for $Q_0(\bar{S}_K, \bar{a}_K)$ and the conditional densities of S_j given the past nonparametric. Yet if the dimension or number of values S can assume and/or the number of decisions is large the curse of dimensionality will result in highly variable estimators.

(2) Note that the above estimation method depends on a correct parameterization of the conditional probability functions, $\bar{p}_K$. Thus we are assuming an overall model for the multivariate distribution of the data that stipulates a parametric model for the regrets, $\bar{\mu}_K$ and a parametric form for the conditional probability functions, $\bar{p}_K$ (all other parts are nonparametric).

(3) In general estimators based directly on the least squares characterization in (13) and/or (14) will not lead to efficient estimators of β. One has several options to remedy this situation. If the dimensionality of the problem is small so that we avoid the curse of dimensionality (e.g. K is small and the status measure can assume only a few values and the possible treatment levels are few) then we can use nonparametric models to estimate each component of the multivariate distribution and then use dynamic programming. If this method is feasible then we do not need to assume a parametric model for the conditional probability functions. Alternately we can adjust the above estimator to achieve double robustness (and a "local" type of efficiency, Robins, 2000). Conceptually this is a straightforward adaptation of Robins' (2000) work on structural nested mean models. A third option is to change the model from a model in which most parts of the multivariate

distribution are left unspecified (i.e., nonparametric) to a model in which the entire multivariate distribution is parametric; then we may use the likelihood to construct maximum likelihood estimators of the regret functions.

4) Simulation Results and Further Discussion

The goal of the simulations is to demonstrate that the estimation methodology proposed here is promising and deserves further investigation. We simulate data from the following prototypical sequentially randomized experiment. This type of experiment would be used to estimate optimal decision rules; rules that maximize academic achievement Y at the end of $K = 10$ intervals. In each interval there are two decisions. The first decision is whether the child should receive special education (1=yes, 0=no). This decision is binary. If the child is recommended for special education then a level 1 or greater special education per day is to be assigned. If the child is not to receive special education then an amount of tutoring per week, 0 or greater is assigned. Each decision should be based on the child's status as assessed at prior time intervals and at the beginning of the present time interval $(S_1, \ldots, S_K)$. In the simulation of the sequentially randomized experiment, the treatment assignment probabilities for the decision as to whether a child should receive special education are uniform on $\{0, 1\}$. The treatment amount assignment probabilities for special education are uniform on $1, 2, 3$ and for reading tutoring are uniform on $0, 1, 2, 3$. Note that although these treatment assignment probabilities do not depend on the past, in a sequentially randomized experiment we can allow the treatment assignment probabilities to depend on the past statuses and treatments.

We divide each interval into two subintervals; in the first subinterval the "yes/no" special education decision is made and in the second subinterval the amount of the appropriate treatment is to be decided. Thus

the effective number of intervals is $2 * K = 20$. The remaining data are simulated as follows. The conditional density of Y, $g(\cdot|\bar{s}_2, \bar{a}_2)$, is a normal, mean zero, variance .64 density. The marginal density of S_1, f_1, is normal with mean $mean_1 = .5$ and variance .01. The conditional density of each S_j given $(\bar{S}_{j-1}, \bar{A}_{j-1})$, $j > 2$ and odd, is normal, mean $mean_j = .5 + .2S_{j-1} - .07A_{j-1}A_{j-2} - .01A_{j-1}(1 - A_{j-2})$, where A_{j-2} assumes 1 or 0 according to whether special education is assigned. The conditional variance of S_j is set to .01. For j even, S_j is set equal to S_{j-1}. Except for the regret functions the terms in the telescoping form of the conditional mean of Y are the ϕ_j's and μ_0. These are set as $\phi_j(\bar{s}_j, \bar{a}_{j-1}) = -5(s_j - mean_j)$ for j odd, and $\mu_0 = 30$. Recall μ_0 is the optimal mean response. There are no ϕ_j terms for j even.

In simulation 1 the true regret for j odd (decide to assign special education or not) is given by $6(a_j - I\{s_j > 5/9\})^2$ and the true regret for j even is given by $1.5a_{j-1}(a_j - 2s_j)^2 + 1.5 * (1 - a_{j-1})(a_j - 5.5s_j)^2$ (the treatment amounts are allowed to be continuous dosage levels). This specification of the regrets means that the simulated mean, $E[Y|\bar{A}_{20} = \bar{a}_{20}, \bar{S}_{20} = \bar{s}_{20}]$ is given by

$$30 - 5 \sum_{j=1, j\ odd}^{20} (s_j - mean_j) - \sum_{j=1, j\ odd}^{20} 6(a_j - I\{s_j > 5/9\})^2$$

$$- \sum_{j=2, j\ even}^{20} 1.5a_{j-1}(a_j - 2s_j)^2 + 1.5 * (1 - a_{j-1})(a_j - 5.5s_j)^2.$$

The regrets are zero at the optimal decision thus, for j odd, $d_j^* = I\{s_j > 5/9\}$ and for j even, $d_j^* = a_{j-1}2s_j + (1 - a_{j-1})5.5s_j$.

In the analysis of each simulated sequentially randomized experiment, we fit a quadratic link ($f(u) = u^2$). In the odd time intervals the fitted regret for the "yes/no" special education decision is

$$\mu_j(\bar{s}_j, \bar{a}_j) = \beta_1 \left(a_j - \frac{e^{30(s_j - \beta_2)}}{1 + e^{30(s_j - \beta_2)}} \right)^2 \tag{15}$$

for $a_j \in \{0,1\}$ (yes = 1, no = 0); that is we approximate the nonsmooth $I\{s_j > \beta_2\}$ by the smooth function $\frac{e^{30(s_j-\beta_2)}}{1+e^{30(s_j-\beta_2)}}$. The choice of 30 is arbitrary; in the future the pros and cons of other choices should be considered. In the even time intervals the fitted regret for the amount of treatment (special education or tutoring) is,

$$\mu_{j,2}(\bar{s}_j, \bar{a}_j) = \beta_4 a_{j-1}\Big(a_j - (\beta_3 + \beta_5 s_j)\Big)^2$$

$$+\beta_7(1 - a_{j-1})\Big(a_j - (\beta_6 + \beta_8 s_j)\Big)^2. \tag{16}$$

So the fitted decision functions are smooth: $d_j = \frac{e^{30(s_j-\beta_2)}}{1+e^{30(s_j-\beta_2)}}$ for j odd and $d_j = a_{j-1}(\beta_3 + \beta_5 s_j) + (1 - a_{j-1})(\beta_6 + \beta_8 s_j)$ for j even.

We conducted a number of simulations; here three are discussed. First for illustrative purposes we provide, in Table 1, estimates of the β's for simulation 1. It is not surprising that β_1 is poorly estimated since we are fitting only an approximation of the optimal decision rule in the odd time intervals.

(Table 1 about here)

Scientific interest is not directly concerned with the accurate estimation of the decision regime but rather is most concerned with the ability of the estimated regime to produce an optimal response. Thus in order to compare the simulation results we provide boxplots and a table that evaluate the mean response to the estimated decision regimes. For each data set in a simulation, we estimate first the β's and then the corresponding decision rule. The estimated rules comprise the estimated regime. Then for each of these estimated decision regimes we calculate the mean response under the estimated treatment regime by Monte Carlo. To be more precise, we generate 10,000 observations (complying with the estimated decision regime) and form the mean response. Thus we have a mean response corresponding to each estimated treatment regime in the simulation. Since our simulations

are of size 1000 data sets, we have 1000 (Monte Carlo estimated) mean responses per simulation. See Table 2 and Figure 1. The first simulation is as above (labeled "Simulation 1"). From Table 2, we see that on average (across estimations of the regimes) the estimated regimes in simulation 1 lead to a mean response of 29.27; recall the optimal mean response is 30. This less-than-optimal performance is attributable to the fact that we are approximating the discontinuous decision rule in the odd time intervals with a smooth function. As a comparison, consider the following simple non-dynamic regime. In the simulations the mean of S_j at each time j is between .4 and .5, indicating that the "average child" would not have been assigned to special education ($.5 < 5/9$). In addition the amount of academic tutoring that is optimally assigned for a child with $S_j = .45$ is 5.5(.45)=2.475. So in our simple non-dynamic regime, all children are assigned 2.475 units of academic tutoring at each time interval. Use of this simple regime results in a average mean response of 15.98. Thus use of the estimated optimal rule as compared to this simple rule results in an average increase of 29.27-15.98=13.29 in the response.

Table 2 and Figure 1 contain results for two further simulations. These two simulations differ from simulation 1 only in the form of their true (i.e. simulated) regrets. In both cases the true link function is nonquadratic (hence the fitted quadratic link is misspecified). Simulation 2 uses data simulated with the link,

$$f(u) = \begin{cases} u^2 & \text{if } u^2 \geq 0.83 \\ 0 & \text{otherwise} \end{cases}$$

in the odd numbered intervals and links,

$$f(u) = \begin{cases} u^2 & \text{if } u^2 \geq 3.33 \\ 0 & \text{otherwise} \end{cases}$$

for both amounts of special education and tutoring, respectively, in the even numbered intervals. From Table 2, under simulation 2, we see that even though the link function is misspecified, the mean response to the estimated optimal regimes is closer to the optimal value of 30 than in simulation 1 (where the link function is correctly specified). This is not surprising since in simulation 2 the true regrets are zero for a range of treatment levels, thus the estimated rules only need to provide a treatment level within a range to produce near-optimal results.

In simulation 3, we consider the opposite situation to simulation 2. In simulation 3 the regrets are "peaked" at the optimal; here the link is

$$f(u) = \begin{cases} |u| & \text{if } u^2 < 1.5 \\ u^2 - 1.5 + \sqrt{1.5} & \text{otherwise} \end{cases}$$

in the odd numbered intervals and links,

$$f(u) = \begin{cases} |u| & \text{if } u^2 < 2.5 \\ u^2 - 2.5 + \sqrt{2.5} & \text{otherwise} \end{cases}$$

for both amounts of special education and tutoring, respectively, in the even numbered intervals. As might be expected misspecification of the link (we fit a quadratic link) results in the poorest mean response of the three simulations. Additionally the variability in mean response across the 1000 estimated optimal regimes more than doubles. Here the "peakedness" of the regret implies that the estimated rules must provide treatment levels very close to the optimal treatment levels to produce a near optimal response. The poor performance and increase in variability is highlighted in Figure 1 by the boxplots of the mean responses.

(Table 2 and Figure 1 about here.)

In general our simulations indicate that the estimation procedure can be sensitive to misspecification of the link function and the use of a smooth

decision rule to approximate a discrete valued decision rule, thus in future we plan to explore the usefulness of more flexible link functions and accurate parameterizations of the rules.

Discussion:

Causal Bayesian networks provide a natural alternative to the method presented here. For example, one constructs a tentative causal Bayesian network (possibly containing unobserved latent variables) that incorporates the assumption that the associated conditional distributions would be the same even if the decisions are set by outside intervention. One "learns" the structure of the causal Bayesian network from the data; i.e. one postulates multivariate models for the group of observed and unobserved variables, estimates parameters and assesses fit. This is an area of intense research. An overview of "learning" the structure of the network with references is provided by Cowell, Dawid, Lauritzen and Spiegelhalter (ch. 11, 1999). See also Heckerman (1998). Then given a particular multivariate model with estimated parameters, one follows the dynamic programming arguments. The dynamic programming steps are computationally difficult; Cooper (1990) shows that probabilistic inference using these types of networks can be NP-hard (problems that cannot necessarily be solved in polynomial time on a sequential computer). Cowell, Dawid, Lauritzen and Spiegelhalter (ch. 11, 1999) discuss the use of local computations and decision potentials designed to reduce the computational burden. It would be most interesting to assess whether the methodology proposed here is competitive. Note that these methods do not directly parameterize the optimal decision rules; furthermore the learning process assumes that there is good scientific information about the distribution of all unobserved variables and about the relationship between the unobserved variables and the observed variables.

Another interesting alternative to the method presented here is the use of Robins' structural nested mean model(Robins, 1986, 1987, 1989, 1997). However in order to form the mean response to a dynamic regime one must (as is the case with Bayesian networks) model the distribution of the each status, S_j as outcomes of past statuses and past treatment.

Lavori and Dawson (2000) propose the use of an approximate Bayesian bootstrap to impute the values of all potential outcomes. After all potential outcomes are imputed, one would calculate the mean response corresponding to each of a variety of dynamic treatment regimes and compare these to find a best dynamic regime. Unfortunately, in the cases we envision the number of time intervals combined with the continuity of the status will preclude the use of the nonparametric approximate Bayesian bootstrap.

This work raises a number of interesting issues. An important practical problem is the appropriate design of sequentially randomized trials to be used for estimating an optimal decision regime. From a statistical standpoint this is a difficult area because practical and ethical considerations might limit the variability in the treatment levels, yet variability in the treatment levels is crucial for high quality estimates. We need to better understand the consequences of low variability in the observed treatment decisions ($\bar{A}_j$) given the past information. Clearly one consequence of low variability and/or a small number of possible values of A_j will be less precise estimation of the rules. A second type of problem that can arise is that in the experiment/observational study, expensive or difficult-to-collect information may have been used in treatment selection. For practical applicability the rules should not depend on this information. For example in the Fast Track study, staff may have used information from detailed summer interviews to assign treatment, however in future summer interviews may not be available. So the goal is to find the rules that optimally use a specified subset of the past information. The work

by van der Laan, Murphy and Robins (2001) should be useful in developing methodology for this problem. A third issue is that we assume decisions are made in discrete time; practically, this means that in any time interval, treatment decisions are made on all or most subjects. However when the timing of the treatment decisions are so variable across subjects that the chance of a decision occurring in any time interval becomes exceedingly small it is better to move to a continuous time framework. It would be very useful to generalize this work to continuous time. Another useful generalization would allow for a time varying response. We could choose to estimate a regime that would optimize a one dimensional summary of the time varying response such as a weighted average of the response with earlier responses contributing less to the average than later responses. This is similar to minimizing discounted expectations in infinite horizon, sequential decision problems (see Bather, 2000, chapter 9 or section 2.1.2 of Bertsekas and Tsitsiklis, 1996). When the one dimensional summary can be expressed as an average, the work presented here should generalize without much alteration.

Because of the similarity in the likelihood between this method and Robins' nested structural mean model, many of Robins' results should generalize to this setting. In particular when the available data is observational, the assumption of no unmeasured confounders is suspect. In this setting Robins has developed sensitivity analyses for the nested structural mean model (Robins, Rotnitzky and Scharfstein, sections 8.1b, 8.2b, 1999). It would be most interesting to develop analyses that examine how the rules would change as one allows for deviations from the no unmeasured confounders assumption.

An additional interesting area was described in the introduction; suppose it is feasible to simulate from the known multivariate distribution. It is unclear whether the methodology presented here can provide the basis for

better computational algorithms that provide approximate optimal regimes. This could be of great utility as the traditional use of a Bayesian network is computationally difficult.

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9) Appendix

Lemma 1: Let (Z_1, Z_2, Z_3) be a random vector where (Z_1, Z_2) are scalars, Z_3 is a m vector and Z_2 is countably discrete. Assume that $E|Z_1|$ is finite. Denote a version of the regular conditional probability density of Z_2 given Z_3 by $p(z_2|z_3)$. Assume that $d : R^m \rightarrow R$ is measurable and that $P[p(d(Z_3)|Z_3) > 0] = 1$. Then any two versions of $E[Z_1|Z_3, Z_2 = d(Z_3)]$ are $a.s.$ equal on the sigma field generated by Z_3.

Proof: By definition of the conditional expectation of Z_1 given Z_3 on the set $\{Z_2 = d(Z_3)\}$, we have that for any B, a set in the sigma field generated by Z_3,

$$\int_{B\cap\{w:Z_2(w)=d(Z_3(w))\}} Z_1 \; dP = \int_{B\cap\{w:Z_2(w)=d(Z_3(w))\}} E[Z_1|Z_3, Z_2 = d(Z_3)] \; dP$$

where $E[Z_1|Z_3, Z_2 = d(Z_3)]$ belongs to the sigma field generated by Z_3 intersected with the set $\{w : Z_2(w) = d(Z_3(w))\}$. Suppose we have two versions of $E[Z_1|Z_3, Z_2 = d(Z_3)]$, on $\{Z_2 = d(Z_3)\}$ these can be written as $h_1(Z_3)$ and $h_2(Z_3)$. By definition,

$$0 = \int_{B\cap\{w:Z_2(w)=d(Z_3(w))\}} \Big(h_1(Z_3) - h_2(Z_3)\Big) \; dP.$$

But this is the same as (by definition of p)

$$0 = \int_B (h_1(Z_3) - h_2(Z_3))p(d(Z_3)|Z_3) \; dP.$$

Since $P[p(d(Z_3)|Z_3) > 0] = 1$, $P[h_1(Z_3) = h_2(Z_3)] = 1$ (not just on the set, $\{w : Z_2(w) = d(Z_3(w))\}$).

Lemma 2: Assume that the range of the treatment decisions, $\bar{A}_K$ is countable and that $E|Y|$ is finite. Assume no unmeasured confounders holds. Assume that the regime, $\bar{d}_K$ is measurable and satisfies (7), where $p_j(a_j|\bar{S}_j, \; \bar{A}_{j-1})$

is a regular conditional density for the conditional distribution of A_j given $\bar{S}_j,\ \bar{A}_{j-1}$. Then the repeated expectation, (5)

$$E\Big[E\Big[\ldots E[E[Y|\bar{S}_K,\ \bar{A}_{K-1},\ A_K = d_K]$$

$$|\bar{S}_{K-1},\ \bar{A}_{K-2},\ A_{K-1} = d_{K-1}]\ldots\Big|S_1,\ A_1 = d_1\Big]\Big]$$

is well defined and is equal to $E[Y(\bar{d}_K)]$.

Proof: For the repeated expectation to be well defined it must be shown to assume a unique (only one!) value. As discussed by Gill and Robins (2001), difficulties occur because the value of each conditional expectation is arbitrary when the conditioning set has probability zero. Assumption (7) and lemma 1 will allow us to show uniqueness. Because each d_j is measurable and by definition of conditional expectations, $E[Y|\bar{S}_K,\ \bar{A}_{K-1},\ A_K = d_K]$, $E[E[Y|\bar{S}_K,\ \bar{A}_{K-1},\ A_K = d_K]\Big|\bar{S}_{K-1},\ \bar{A}_{K-2},\ A_{K-1} = d_{K-1}]$, etc., are defined $a.s.\ P$. Using lemma 1 and (7), (e.g. in first case equate Y with Z_1, ($\bar{S}_K$, $\bar{A}_{K-1}$) with Z_3 and equate A_K with Z_2) we see that conditional expectation is uniquely defined $a.s.\ P$. Thus (5) is well defined.

To see that (5) is equal to $E[Y(\bar{d}_K)]$, first note that $E[Y|\bar{S}_K,\ \bar{A}_{K-1},\ A_K = d_K]$ is equal to $E[Y(\bar{A}_{K-1}, d_K)|\bar{S}_K,\ \bar{A}_{K-1},\ A_K = d_K]$ $a.s.$ by definition of Y. But O_{sr} is independent of A_K conditionally on ($\bar{S}_K$, $\bar{A}_{K-1}$), thus the above conditional expectation is equal to $E[Y(\bar{A}_{K-1}, d_K)|\bar{S}_K,\ \bar{A}_{K-1}]$ $a.s.$ Thus (5) is equal to

$$E\Big[E\Big[\ldots E[E[Y(\bar{A}_{K-1}, d_K)|\bar{S}_K,\ \bar{A}_{K-1}]$$

$$|\bar{S}_{K-1},\ \bar{A}_{K-2},\ A_{K-1} = d_{K-1}]\ldots\Big|S_1,\ A_1 = d_1\Big]\Big].$$

Next the repeated expectation, $E[E[Y(\bar{A}_{K-1}, d_K)|\bar{S}_K,\ \bar{A}_{K-1}]|\bar{S}_{K-1},\ \bar{A}_{K-2},\ A_{K-1} = d_{K-1}]$ is equal to $E[Y(\bar{A}_{K-1}, d_K)|\bar{S}_{K-1},\ \bar{A}_{K-2},\ A_{K-1} = d_{K-1}]$ $a.s.$ Now we

repeat the arguments made before; that is, first use the definition of Y then since O_{sr} is independent of A_{K-1} conditionally on $(\bar{S}_{K-1},\ \bar{A}_{K-2})$, the above conditional expectation becomes, $E[Y(\bar{A}_{K-2}, d_{K-1}, d_K)|\bar{S}_{K-1},\ \bar{A}_{K-2}]$. Repeated use of these arguments proves that (5) is indeed equal to $E[Y(\bar{d}_K)]$.

Lemma 3: Let Z_1 be a random variable, Z_3, a random m vector and Z_2, a random variable with range $\mathcal{A}$ where $\mathcal{A}$ is countable. Assume that $E|Z_1|$ is finite. Denote a version of the regular conditional density of Z_2 given Z_3 by $p(z_2|z_3)$. Then given $\epsilon > 0$ there exists a measurable function d such that,

$$E[Z_1|Z_3, Z_2 = d(Z_3)] \geq \sup_{a:p(a|Z_3)>0} E[Z_1|Z_3, Z_2 = a] - \epsilon$$

a.e. P.

Proof: Without loss of generality assume that $\mathcal{A}$ is the positive integers. Since $E|Z_1|$ is finite we may choose a version of $E[Z_1|Z_3 = z_3, Z_2 = j]$ that is finite everywhere. Consider the set of positive integers, j for which $E[Z_1|Z_3 = z_3, Z_2 = j] \geq \sup_{i:p(i|z_3)>0} E[Z_1|Z_3 = z_3, Z_2 = i] - \epsilon$ and $p(j|z_3) > 0$. Let $d(z_3)$ be the minimum integer in this set. Then we have $\{z_3 : d(z_3) > j\} = \{z_3 : \max_{i \leq j, p(i|z_3)>0} E[Z_1|Z_3 = z_3, Z_2 = i] < \sup_{a:p(a|z_3)>0} E[Z_1|Z_3 = z_3, Z_2 = a] - \epsilon\}$. This set is measurable for all values of j thus d is measurable.

Proof of Theorem 1: First (5) is no greater than

$$E\Big[E\Big[\ldots E[J_0(\bar{S}_K, \bar{A}_{K-1})|\bar{S}_{K-1},\ \bar{A}_{K-2},\ A_{K-1} = d_{K-1}]\ldots\Big|S_1,\ A_1 = d_1\Big]\Big].$$

This is because $p_K(d_K(\bar{S}_K, \bar{A}_{K-1})|\bar{S}_K, \bar{A}_{K-1}) > 0$ *a.s.* and d_K must take values in $\{a_K : p_K(a_K|\bar{S}_K, \bar{A}_{K-1}) > 0\}$. Let $\epsilon > 0$. Furthermore use lemma 3 to see that (9) is at least as large as

$$\sup_{\bar{d}_{K-1} \in D_P} E\Big[E\Big[\ldots E[J_0(\bar{S}_K, \bar{A}_{K-1})|\bar{S}_{K-1},\ \bar{A}_{K-2},\ A_{K-1} = d_{K-1}]\ldots\Big|S_1,\ A_1 = d_1\Big]\Big] - \epsilon$$

because D_P includes all measurable rules, d_K depending on $\bar{S}_K, \bar{A}_{K-1}$ with $p_K(d_K(\bar{S}_K, \bar{A}_{K-1})|\bar{S}_K, \bar{A}_{K-1}) > 0$ *a.s.* Thus (9) is within ϵ of the first term in the former display.

Evaluating the repeated expectation, the first term of the previous display is

$$\sup_{\bar{d}_{K-1} \in D_P} E\Big[E\Big[\ldots E[Q_1(\bar{S}_{K-1}, \bar{A}_{K-2}, d_{K-1})|\bar{S}_{K-2}, \bar{A}_{K-3}, A_{K-2} = d_{K-2}]\ldots\Big|S_1,\ A_1 = d_1\Big]\Big]. \tag{17}$$

Similarly we note that (17) is within ϵ of

$$\sup_{\bar{d}_{K-2} \in D_P} E\Big[E\Big[\ldots E[J_1(\bar{S}_{K-1}, \bar{A}_{K-2})|\bar{S}_{K-2}, \bar{A}_{K-3}, A_{K-2} = d_{K-2}]\ldots\Big|S_1,\ A_1 = d_1\Big]\Big]$$

and thus this display is within 2ϵ of (9). Finish the proof by repeating this argument and recognizing that ϵ is arbitrary .

Proof of Theorem 2: We only need (13) to hold for $\bar{m}_K = \bar{\mu}_{0K}$. Note that $E[\mu_K(\bar{S}_K, \bar{A}_K)|\bar{S}_K, \bar{A}_{K-1}] = \sum_a \mu_K(\bar{S}_K, \bar{A}_{K-1}, a)p_K(a|\bar{S}_K, \bar{A}_{K-1})$. Consider the Kth inequality

$$E\left[Y + \sum_{l=1}^{K} \mu_l(\bar{S}_l, \bar{A}_l) - E[\mu_K(\bar{S}_K, \bar{A}_K)|\bar{S}_K, \bar{A}_{K-1}]\right]^2 \leq$$

$$E\left[Y + \sum_{l=1}^{K-1} \mu_l(\bar{S}_l, \bar{A}_l) + \mu_{0K}(\bar{S}_K, \bar{A}_K) - E[\mu_{0K}(\bar{S}_K, \bar{A}_K)|\bar{S}_K, \bar{A}_{K-1}]\right]^2$$

Combining terms we have

$$2E\left[Y + \sum_{l=1}^{K-1} \mu_l(\bar{S}_l, \bar{A}_l) + \mu_{0K}(\bar{S}_K, \bar{A}_K) - E[\mu_{0K}|\bar{S}_K, \bar{A}_{K-1}]\right]$$

$$\cdot \Big[\mu_K(\bar{S}_K, \bar{A}_K) - \mu_{0K}(\bar{S}_K, \bar{A}_K) - E[\mu_K - \mu_{0K}|\bar{S}_K, \bar{A}_{K-1}]\Big]$$

$$+E\left[\mu_K(\bar{S}_K,\bar{A}_K)-\mu_{0K}(\bar{S}_K,\bar{A}_K)-E[\mu_K-\mu_{0K}|\bar{S}_K,\bar{A}_{K-1}]\right]^2 \;\leq\; 0.$$

Since the second part of the product in the first term has conditional mean zero, the first term simplifies to yield,

$$2E\left[Y+\mu_{0K}(\bar{S}_K,\bar{A}_K)\right]\left[\mu_K(\bar{S}_K,\bar{A}_K)-\mu_{0K}(\bar{S}_K,\bar{A}_K)-E[\mu_K-\mu_{0K}|\bar{S}_K,\bar{A}_{K-1}]\right]$$

$$+E\left[\mu_K(\bar{S}_K,\bar{A}_K)-\mu_{0K}(\bar{S}_K,\bar{A}_K)-E[\mu_K-\mu_{0K}|\bar{S}_K,\bar{A}_{K-1}]\right]^2 \;\leq\; 0.$$

Recall that $\mu_{0K}(\bar{S}_K,\bar{A}_K)$ is equal to $-E[Y|\bar{S}_K,\bar{A}_K]$ plus a term constant in A_K thus the first term is identically zero and we have

$$E\left[\mu_K(\bar{S}_K,\bar{A}_K)-\mu_{0K}(\bar{S}_K,\bar{A}_K)-E[\mu_K-\mu_{0K}|\bar{S}_K,\bar{A}_{K-1}]\right]^2 \;\leq\; 0.$$

implying that the quantity inside the expectation is $a.s.$ equal to zero. Thus,

$$E\left(\left[\mu_K(\bar{S}_K,\bar{A}_K)-\mu_{0K}(\bar{S}_K,\bar{A}_K)-E[\mu_K-\mu_{0K}|\bar{S}_K,\bar{A}_{K-1}]\right]^2\Big|\bar{S}_K,\bar{A}_{K-1}\right]=0\ a.s.$$

That is

$$\sum_a\left[\mu_K(\bar{S}_K,\bar{A}_{K-1},a)-\mu_{0K}(\bar{S}_K,\bar{A}_{K-1},a)-E[\mu_K-\mu_{0K}|\bar{S}_K,\bar{A}_{K-1}]\right]^2 p_K(a|\bar{S}_K,\bar{A}_{K-1})=0$$

$a.s.$ Fix a sample point in this set of probability 1. Then for each a with $p_K(a|\bar{S}_K,\bar{A}_{K-1})>0$ we have

$$\mu_{0K}(\bar{S}_K,\bar{A}_{K-1},a)-\mu_K(\bar{S}_K,\bar{A}_{K-1},a)=E[\mu_{0K}-\mu_K|\bar{S}_K,\bar{A}_{K-1}].$$

Recall that the supremum of $\mu_{0K}(\bar{S}_K,\bar{A}_{K-1},a)$ over such a is zero and by assumption the same holds for μ_K. Thus $E[\mu_{0K}-\mu_K|\bar{S}_K,\bar{A}_{K-1}]=0$ and

$$\mu_{0K}(\bar{S}_K,\bar{A}_{K-1},a)-\mu_K(\bar{S}_K,\bar{A}_{K-1},a)=0.$$

We have $\mu_{0K}=\mu_K$ with probability one.

Next we consider (13) for $j = K-1$ and $\bar{m}_{K-1} = \bar{\mu}_{0,K-1}$. The proof is virtually identical to the above. Using the just shown result that $\mu_{0K} = \mu_K$, we have

$$E\left[Y + \sum_{l=1}^{K-1} \mu_l(\bar{S}_l, \bar{A}_l) + \mu_{0K}(\bar{S}_K, \bar{A}_K) - E[\mu_{K-1}|\bar{S}_{K-1}, \bar{A}_{K-2}]\right]^2 \leq$$

$$E\left[Y + \sum_{l=1}^{K-2} \mu_l(\bar{S}_l, \bar{A}_l) + \sum_{l=K-1}^{K} \mu_{0l}(\bar{S}_l, \bar{A}_l) - E[\mu_{0,K-1}|\bar{S}_{K-1}, \bar{A}_{K-2}]\right]^2$$

Combining terms as before,

$$2E\left[Y + \sum_{l=1}^{K-2} \mu_l(\bar{S}_l, \bar{A}_l) + \sum_{l=K-1}^{K} \mu_{0l}(\bar{S}_l, \bar{A}_l) - E[\mu_{0,K-1}|\bar{S}_{K-1}, \bar{A}_{K-2}]\right]$$

$$\cdot \left[\mu_{K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) - \mu_{0,K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) - E[\mu_{K-1} - \mu_{0,K-1}|\bar{S}_{K-1}, \bar{A}_{K-2}]\right]$$

$$+E\left[\mu_{K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) - \mu_{0,K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) - E[\mu_{K-1} - \mu_{0,K-1}|\bar{S}_{K-1}, \bar{A}_{K-2}]\right]^2 \leq 0.$$

Since the second part of the product in the first term has conditional mean zero, the first term simplifies to yield,

$$2E\left[Y + \mu_{0,K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) + \mu_{0K}(\bar{S}_K, \bar{A}_K)]\right]$$

$$\cdot \left[\mu_{K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) - \mu_{0,K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) - E[\mu_{K-1} - \mu_{0,K-1}|\bar{S}_{K-1}, \bar{A}_{K-2}]\right]$$

$$+E\left[\mu_{K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) - \mu_{0,K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) - E[\mu_{K-1} - \mu_{0,K-1}|\bar{S}_{K-1}, \bar{A}_{K-2}]\right]^2 \leq 0.$$

Since $\mu_{0,K-1}(\bar{S}_{K-1}, \bar{A}_{K-1})$ is equal to $-E[Y+\mu_{0,K}(\bar{S}_K, \bar{A}_K)|\bar{S}_{K-1}, \bar{A}_{K-1}]$ plus a term constant in A_{K-1} the first term is zero. We have,

$$E\left[\mu_{K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) - \mu_{0,K-1}(\bar{S}_{K-1}, \bar{A}_{K-1}) - E[\mu_{K-1} - \mu_{0,K-1}|\bar{S}_{K-1}, \bar{A}_{K-2}]\right]^2 = 0.$$

implying that the quantity inside the expectation is $a.s.$ equal to zero. As in the arguments for $j = K$ this implies that $\mu_{0,K-1} = \mu_{K-1}$ with probability one.

Continuing in this fashion we see that $\bar{\mu}_{0K} = \bar{\mu}_K$ with probability one. Also it is easy to see that we can replace the $\sum_{l=1}^{K}$ by $\sum_{l\geq j}^{K}$ and the sum $\sum_{l=1,l\neq j}^{K}$ by $\sum_{l>j}^{K}$ and the same result holds.

Variance of $\widehat{\beta}$: This estimator can be used when the regrets and optimal decisions are smooth functions of β. For a p column vector, say V, denote VV^T by $V^{\otimes 2}$. Also denote the first derivative with respect to α of $p_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \alpha)$ by $\dot{p}_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \alpha)$ and set $S_\alpha(\bar{S}_K, \bar{A}_K; \alpha)$
$= \sum_{j=1}^{K} \dot{p}_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \alpha)/p_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \alpha)$. Denote the second derivative with respect to α of $\mathbb{P}_n\left[\sum_{j=1}^{K} \log p_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \alpha)\right]$ and evaluated at $\alpha = \widehat{\alpha}_n$ by $-\widehat{I}_{\alpha\alpha}$. Denote the first derivative of $\mu_j(\bar{S}_j, \bar{A}_j; \beta)$ with respect to β by $\dot{\mu}_j(\bar{S}_j, \bar{A}_j; \beta)$. Set $\widehat{c}(\beta, \alpha)$ equal to

$$\frac{-1}{K}\sum_{j=1}^{K}\mathbb{P}_n\left[Y + \sum_{l=1}^{K}\mu_l(\bar{S}_l, \bar{A}_l; \beta) - \sum_{a_j}\mu_j(\bar{S}_j, \bar{A}_{j-1}, a_j; \beta)p_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \alpha)\right],$$

set $S_\beta(Y, \bar{S}_K, \bar{A}_K; \widehat{\beta}_n, \widehat{\alpha}_n)$ to

$$\sum_{j=1}^{K}\left[Y + \widehat{c}(\widehat{\beta}_n, \widehat{\alpha}_n) + \sum_{l=1}^{K}\mu_l(\bar{S}_l, \bar{A}_l; \widehat{\beta}_n) - \sum_{a_j}\mu_j(\bar{S}_j, \bar{A}_{j-1}, a_j; \widehat{\beta}_n)p_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \widehat{\alpha}_n)\right]$$

$$\times\left[\frac{\partial}{\partial\beta}\widehat{c}(\beta, \widehat{\alpha}_n)|_{\beta=\widehat{\beta}_n} + \dot{\mu}_j(\bar{S}_j, \bar{A}_j; \widehat{\beta}_n) - \sum_{a_j}\dot{\mu}_j(\bar{S}_j, \bar{A}_{j-1}, a_j; \widehat{\beta}_n)p_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \widehat{\alpha}_n)\right]$$

and set $-\widehat{I}_{\beta\alpha}$ equal to

$$\sum_{j=1}^{K}\mathbb{P}_n\left[\dot{\mu}_j(\bar{S}_j, \bar{A}_j; \widehat{\beta}_n) - \sum_{a_j}\dot{\mu}_j(\bar{S}_j, \bar{A}_{j-1}, a_j; \widehat{\beta}_n)p_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \widehat{\alpha}_n)\right]$$

$$\times \left[\frac{\partial}{\partial \alpha} \widehat{c}(\widehat{\beta}_n, \alpha)|_{\alpha=\widehat{\alpha}_n} - \sum_{a_j} \mu_j(\bar{S}_j, \bar{A}_{j-1}, a_j; \widehat{\beta}_n) \dot{p}_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \widehat{\alpha}_n) \right]^T$$

$$- \sum_{j=1}^{K} \mathbb{P}_n \left[Y + \widehat{c}(\widehat{\beta}_n, \widehat{\alpha}_n) + \sum_{l=1}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \widehat{\beta}_n) - \sum_{a_j} \mu_j(\bar{S}_j, \bar{A}_{j-1}, a_j; \widehat{\beta}_n) p_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \widehat{\alpha}_n) \right]$$

$$\times \left[\sum_{a_j} \dot{\mu}_j(\bar{S}_j, \bar{A}_{j-1}, a_j; \widehat{\beta}_n) \dot{p}_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \widehat{\alpha}_n)^T \right].$$

Lastly set $-\widehat{I}_{\beta\beta}$ equal to,

$$\sum_{j=1}^{K} \mathbb{P}_n \left[\frac{\partial}{\partial \beta} \widehat{c}(\beta, \widehat{\alpha}_n)|_{\beta=\widehat{\beta}_n} + \sum_{l=1}^{K} \dot{\mu}_l(\bar{S}_l, \bar{A}_l; \widehat{\beta}_n) - \sum_{a_j} \dot{\mu}_j(\bar{S}_j, \bar{A}_{j-1}, a_j; \widehat{\beta}_n) p_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \widehat{\alpha}_n) \right]$$

$$\times \left[\dot{\mu}_j(\bar{S}_j, \bar{A}_j; \widehat{\beta}_n) - \sum_{a_j} \dot{\mu}_j(\bar{S}_j, \bar{A}_{j-1}, a_j; \widehat{\beta}_n) p_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \widehat{\alpha}_n) \right].$$

For sample of n subjects we estimate the asymptotic variance of $\widehat{\beta}$ by

$$(1/n)\widehat{I} = (1/n)\widehat{I}_{\beta\beta}^{-1} \mathbb{P}_n [S_\beta(Y, \bar{S}_K, \bar{A}_K; \widehat{\beta}_n, \widehat{\alpha}_n) + \widehat{I}_{\beta\alpha}\widehat{I}_{\alpha\alpha}^{-1} S_\alpha(\bar{S}_K, \bar{A}_K; \widehat{\alpha}_n)]^{\otimes 2} \left(\widehat{I}_{\beta\beta}^{-1}\right)^T.$$

Variance of $\widehat{\mu}_0$: An estimator of the asymptotic variance of $\widehat{\mu}_0$ is given by

$$(1/n)\mathbb{P}_n \left[\sum_{j=1}^{K} \mu_j(\bar{S}_j, \bar{A}_j; \widehat{\beta}_n) + Y + \widehat{I}_{0\beta}\widehat{I}^{-1} [S_\beta(Y, \bar{S}_K, \bar{A}_K; \widehat{\beta}_n, \widehat{\alpha}_n) + \widehat{I}_{\beta\alpha}\widehat{I}_{\alpha\alpha}^{-1} S_\alpha(\bar{S}_K, \bar{A}_K; \widehat{\alpha}_n)] \right]^2$$

where $\widehat{I}_{0\beta} = \mathbb{P}_n \left[\sum_{j=1}^{K} \dot{\mu}_j(\bar{S}_j, \bar{A}_j; \widehat{\beta}_n) \right]^T$.

Table 1. Estimates of Parameters in the Decision Regime: Simulation 1

True β	Avg. $\hat{\beta}$	Std. Err.	Avg. Est. Std. Err.
6.0	6.89	0.210	0.210
0.56	0.56	0.002	0.002
0.0	0.05	0.184	0.181
1.5	1.50	0.125	0.125
2.0	2.01	0.255	0.247
0.0	0.06	0.128	0.125
1.5	1.48	0.078	0.083
5.5	5.54	0.358	0.358

Simulations of 1000 data sets of size 1000.

Table 2. Descriptive Statistics for the Mean Response to each of 1000 Estimated Treatment Regimes

	$Simulation1$	$Simulation2$	$Simulation3$
Mean	29.27	29.54	28.22
Median	29.27	29.54	28.29
Std.Dev.	0.19	0.16	0.47

The mean response is evaluated using 10,000 Monte Carlo repetitions. The optimal mean response is 30.

Figure 1. Mean Responses for Estimated Optimal Regimes