Semiparametric Statistical Methods for Causal Inference with Stochastic Treatment Regimes

by

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Abstract

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Nearly a century ago, the foundations of modern statistics laid the groundwork for a science of causality. Today, causal inference is central to the study of the most impactful questions at the intersection of science and policy: By what mechanisms do novel therapeutics mitigate relapse in addiction disorders? How do immunobiological markers mediate action mechanisms of vaccines? While randomization provides "gold standard" tools for quantifying causal effects, such trials are costly and limit the scope of scientific inquiry. Thus, techniques for statistical causal inference with complex, observational data are critical to today's, and tomorrow's, scientific endeavors.

Observational studies obviate many of the shortcomings of randomized trials but bring their own challenges and promises. Without randomization, causal inference is plagued by confounding: vaccinees may be more likely to engage in risky behaviors and patients assigned a candidate therapeutic are not uniformly "treated" due to clinician heterogeneity. Adjusting for potential confounders is a daunting challenge in an era where studies routinely measure numerous high-dimensional characteristics. While observational studies empower scientists to assess mechanistic, path-specific causal effects that *cannot be learned* with randomized data, tools from non/semi-parametric statistical theory and machine learning are needed to avoid imposing unrealistic assumptions and novel causal effect estimands are required to better address mechanistic questions.

Causal inference methodology is critical to answering real-world scientific questions, but traditional approaches make too many simplifying assumptions. By ignoring biased sampling designs, continuous-valued treatments, and confounding of path-specific effects, standard techniques fall

short of empowering mechanistic discovery. Such techniques often require *a priori* modeling assumptions unsupported by domain knowledge, limiting their utility for real-world data analysis.

This dissertation, divided into six chapters, extends theory and methods for non/semi-parametric causal inference in settings with continuous treatments, with particular attention paid to issues emerging from biased sampling designs and path-specific causal effects. Throughout, *stochastic treatment regimes*, or stochastic interventions, are leveraged to provide a single, unifying framework for formalizing such causal inference problems.

Chapter 1 considers estimation of the generalized propensity score, a quantity critical to estimating the causal effects of stochastic interventions. We formulate algorithms for flexibly estimating it using the highly adaptive lasso, a nonparametric regression estimator. We then develop a novel inverse probability weighted estimator of these types of causal effects and demonstrate its ability to achieve the non/semi-parametric efficiency bound in numerical experiments.

Chapter 2 focuses on the application of the causal effects of stochastic interventions in real-world studies that rely upon outcome-dependent two-phase sampling (e.g., case-cohort designs). The work includes a methodological advance that unites techniques for estimating the causal effects of stochastic interventions with corrections for biased sampling, allowing for these complex causal parameters to be efficiently estimated under such designs. Motivated by the aims of an HIV vaccine efficacy trial, this contribution allows researchers to probe how vaccination-induced immunogenicity of candidate immune correlates of protection may best be modulated by future vaccines, and the proposed methodology is demonstrated through a re-analysis of this trial's data.

The COVID-19 pandemic took the world by storm during the final year of this work. Chapter 3 generalizes the methodology proposed in Chapter 2 to help maximize what can be learned from the critical scientific questions posed by vaccine trials to combat COVID-19. These developments have served as part of the immune correlates analyses of the COVID-19 Prevention Network, a large-scale collaboration organized by the National Institute of Allergy and Infectious Diseases.

Chapter 4 examines path-specific causal effects formulated via stochastic interventions and broadens the scope of the general framework of causal mediation analysis. In particular, this work introduces a new class of direct and indirect effect parameters robust to intermediate confounding. Developing non/semi-parametric efficient techniques for the flexible estimation of these path-specific effects facilitates their use in quantifying mechanistic knowledge and extracting actionable insights from modern, large-scale studies.

Chapter 5 discusses the role of open source software and reproducible research in statistics and allied computational sciences. Three software packages for statistical causal inference, each implementing elements of the statistical methodology discussed prior, are introduced.

Chapter 6 concludes with a discussion of interesting avenues that may motivate future research.

To my parents, whose support and encouragement made it possible to pursue this journey.

To my brother, Aria, who enriched and challenged my style of thinking with stimulating conversations, and whose work ethic and intellectual curiosity have been an inspiration.

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Chapter 1

Generalizing the Propensity Score

Continuous treatment variables have posed a significant challenge for causal inference, both in the formulation and identification of scientifically meaningful effects and in their robust estimation. Traditionally, focus has been placed on techniques applicable to binary or categorical treatments with few levels, allowing for the application of propensity score-based methodology with relative ease. Efforts to accommodate continuous treatments introduced the generalized propensity score, yet estimators of this nuisance parameter commonly utilize parametric regression strategies that sharply limit the flexibility and robustness of classical inverse probability weighted estimators of causal effect parameters. We present and investigate novel, flexible estimators of the generalized propensity score, based on a recently developed nonparametric regression function that converges at a fast rate to the target functional. Using our proposed estimator, we demonstrate the construction of nonparametric inverse probability weighted estimators of a class of causal effect estimands tailored to continuous treatments. We outline non-restrictive conditions and selection procedures for applying undersmoothing to our generalized propensity score estimators to develop inverse probability weighted estimators capable of achieving the nonparametric efficiency bound, demonstrating the attainability of these properties in numerical experiments. Open source software implementing our proposed estimation techniques, the `haldensify` `R` package, is briefly introduced.

1.1 Introduction

From the biomedical and health sciences to the social and economic sciences, research efforts often aim to quantify the causal impacts of intervening on continuous-valued treatments. Evaluating the causal effects of such treatments opens the door to addressing myriad complex scientific questions; examples include evaluating the impacts of increased physical exercise on aging in the

elderly [37], reductions in surgical operating time on post-surgical health outcomes [68], changes in vaccination-induced immunologic response activity on disease risk [78], and how total nurse hours per patient affects the risk of hosptial readmission [108]. The evaluation of the causal effects of continuous treatments leads most naturally to scientific parameters that capture dose-response phenomena, such as the well-studied *causal* dose-response curve [e.g., 89, 40, 92].

Unfortunately, the definition of counterfactual parameters for continuous treatments requires significant care. While counterfactual random variables provide a formalism to describe the values an outcome measurement would have taken if, possibly counter-to-fact, a specific level of the treatment had been assigned (instead of that observed), for continuous treatments, the set of enumerable counterfactuals grows quickly intractable. A prominent simplification is coarsening, or discretization into countably few categories. The adoption of such a strategy narrows the set of relevant counterfactual values of the outcome variable, allowing for the subsequent straightforward application of standard, well-studied parameters (e.g., the average treatment effect) and corresponding well-established estimators. Despite their convenience, such coarsening strategies come at the cost of ignoring fundamental scientific knowledge about the system under study.

The consideration of continuous treatment variables leads to a host of complications for the formulation, identification, and estimation of causal effects, usually necessitating non-standard techniques for their resolution. While the analysis of the causal dose-response curve and related estimands brings with it many statistical challenges (e.g., a lack of asymptotic linearity), several recent efforts have borne fruit: Díaz and van der Laan [40] proposed a doubly robust substitution estimator of the dose-response curve's risk, Kennedy et al. [92] developed an estimation strategy based on locally linear smoothing, van der Laan, Bibaut, and Luedtke [169] considered cross-validated targeted minimum loss estimation of a general class of non-standard parameters (including the dose-response curve as an example), and Westling, Gilbert, and Carone [191] contributed a monotone nonparametric estimator of the dose-response curve. These methodological advances notwithstanding, deploying such approaches may yet require the consideration of scientifically unrealistic counterfactual variables and infeasible intervention schedules for generating them. Accordingly, alternative frameworks for working with continuous treatments have been pursued.

One such framework is based on the causal effects of *stochastic* interventions [155, 37, 68, 186, 198], which consider setting the post-intervention treatment level to a random draw from a user-specified distribution. This approach makes for a highly flexible means of defining counterfactual random variables — indeed, even static interventions are a special case in which the post-intervention treatment value is drawn from a degenerate distribution with all mass placed on a single treatment level. To ensure scientifically meaningful counterfactuals, careful attention must be paid to defining the particular distribution from which the post-intervention treatment value is drawn. A popular strategy draws post-intervention treatment values from a modification of the

natural treatment distribution. Counterfactuals defined in this way may be better aligned with plausible future interventions that may be scientifically engineered. Recent efforts have provided several candidate approaches [37, 68, 198, 91] for identifying and estimating the causal effects of stochastic interventions. The framework of stochastic interventions is further distinguished by its generalizability, which has allowed for recent extensions to complex settings involving mediating variables [35, 42, 79].

While stochastic interventions appear a promising avenue, estimation strategies formulated within this framework run aground of a familiar issue: evaluation of the *generalized* propensity score [2] (i.e., conditional treatment density given covariates), analogous to the propensity score [144], is required. The generalized propensity score has been a common ingredient for evaluating the causal effects of continuous treatments, both within and without the stochastic intervention framework. For example, Robins, Hernán, and Brumback [138] posited a marginal structural model of the outcome process and used inverse probability weighted estimation of its parameters, which include the generalized propensity score. Avoiding direct modeling of the outcome, Hirano and Imbens [81] formulated an adjustment procedure, based on covariate-balancing, for estimation of the generalized propensity score. Along similar lines, Imai and Van Dyk [88] considered direct extensions of the propensity score to multi-level treatments, while Galvao and Wang [56] proposed a two-step semiparametric-efficient estimator utilizing inverse weighting based on the generalized propensiy score. Despite its prevalence, most proposals rely upon restrictive parametric modeling assumptions to facilitate estimation of the generalized propensity score, though, more recently, flexible estimators leveraging advances in machine learning have received relatively meager attention [39, 201].

In the present work, we discuss several flexible semiparametric strategies for estimation of the generalized propensity score, all presented within the context of evaluating the causal effects of stochastic interventions on continuous treatments. From among these proposals, we highlight a nonparametric estimator of the conditional treatment density based on pooled hazard regression. Building upon our proposed generalized propensity score estimator, we develop and evaluate a unique inverse probability weighted estimator capable of achieving levels of efficiency usually attainable only with doubly robust estimation frameworks. We additionally discuss open source software packages, `haldensify` [74] and `sl3` [31], for the `R` statistical programming environment [133], that facilitate implementation of our generalized propensity score estimators and efficient inverse probability weighted estimators.

1.2 Preliminaries

Problem Formulation and Notation

Let $W \in \mathcal{W}$ denote a vector of baseline covariates, $A \in \mathcal{A}$ a real-valued continuous treatment, and $Y \in \mathcal{Y}$ an outcome of interest. To formalize the causal question of interest, we introduce a nonparametric structural equation model (NPSEM) to describe the data-generating process [117]. Specifically, we assume the following system of structural equations generates the observed data:

$$W = f_W(U_W); A = f_A(W, U_A); Y = f_Y(A, W, U_Y),$$

where $\{f_W, f_A, f_Y\}$ are deterministic functions, and $\{U_W, U_A, U_Y\}$ are exogenous random variables. Importantly, the NPSEM implies a model for the distribution of counterfactual random variables, which are generated by specific interventions on the data-generating process. Within the framework of potential outcomes [112, 146, 148, 147], the full (unobserved) data unit may be expressed $X = (W, Y_a : a \in \mathcal{A})$, where the counterfactuals Y_a represent outcomes corresponding to each possible value in the support of the treatment $\mathcal{A}$. Our focus will be the estimation of counterfactual treatment parameters that are themselves functionals of X.

Consider the observed data as having been generated by typical cohort sampling, where the data on a single observational unit O is denoted $O = (W, A, Y)$. We use P_0 to denote the distribution of O, and, assuming access to n independent copies of O, P_n for the empirical distribution of the n copies $O_1, \ldots, O_n$. Assuming only that P_0 is an element of the nonparametric statistical model $\mathcal{M}$, i.e., $P_0 \in \mathcal{M}$, we avoid placing any restrictions on the form of P_0. We use p_0 to denote the density of O, which evaluated on a typical observation o, is

$$p_0(o) = q_{0,Y}(y \mid A = a, W = w) g_{0,A}(a \mid W = w) q_{0,W}(w) \ ,$$

where $q_{0,Y}$ denotes the conditional density of Y given $\{A, W\}$ with respect to some dominating measure, $g_{0,A}$ the conditional density of A given W with respect to dominating measure μ, and $q_{0,W}$ the density of W with respect to dominating measure ν.

Counterfactual quantities of interest may be defined by specific interventions that alter the structural equation f_A and insert post-intervention treatment values of interest in place of the values that would be naturally generated by f_A. A familiar example comes in the form of *static interventions*, which are defined by replacing f_A with a specific value, selected *a priori*, $a \in \mathcal{A}$. When the cardinality of $\mathcal{A}$ is small — that is, there are few treatment values — contrasts of the counterfactual means of static interventions under each $a \in \mathcal{A}$ can prove useful. On the other hand, when the cardinality of $\mathcal{A}$ is large, or when A is continuous-valued, the evaluation of many such counterfactual means is of questionable scientific relevance and, besides, statistically challenging.

A *stochastic intervention* modifies the value A would naturally assume, $f_A(W, U_A)$, by replacing it with a draw from a post-intervention distribution $\tilde{g}_{0,A}(\cdot \mid W)$ (n.b., the zero subscript emphasizes that this distribution may depend on the true, but unknown, data-generating distribution P_0). Of course, a stochastic intervention may be designed to collapse into a static intervention simply by selecting the post-intervention distribution $\tilde{g}_{0,A}(\cdot \mid W)$ to be degenerate, so as to place all mass on a single point $a \in \mathcal{A}$.

Díaz and van der Laan [37] described a stochastic intervention that draws A from a distribution such that $\tilde{g}_{0,A}(a \mid W) = g_{0,A}(d^{-1}(a, w) \mid W)$, indexed by a user-supplied *shifting* function, and a given $a \in \mathcal{A}$. Shortly thereafter, Haneuse and Rotnitzky [68] showed that estimation of the causal effect of this shifting intervention is equivalent to that of an intervention modifying the value A would naturally assume according to a regime $d(A, W)$ under the assumption of *piecewise smooth invertibility*:

A1 (Piecewise smooth invertibility)**.** For each $w \in \mathcal{W}$, assume that the interval $\mathcal{I}(w) = (l(w,), u(w))$ may be partitioned into subintervals $\mathcal{I}_{\delta,j}(w) : j = 1, \ldots, J(w)$ such that $d(a, w)$ is equal to some $d_j(a, w)$ in $\mathcal{I}_{\delta,j}(w)$ and $d_j(\cdot, w)$ has inverse function $h_j(\cdot, w)$ with derivative $h'_j(\cdot, w)$.

Assumption A1 can be used to show that the intervention may be interpreted on the individual level [198]. Importantly, the regime $d(A, W)$ may depend on both covariates W and the treatment A that would be assigned in the absence of the regime; consequently, this has been termed a *modified treatment policy* (MTP). Both Haneuse and Rotnitzky [68] and Díaz and van der Laan [38] were motivated by counterfactual questions of modifying an intervention, the former seeking to evaluate the effect on patient health of reducing surgical operating time and the latter by the effect of adjusting prescribed exercise regimens based on the athletic habits of patients. Conveniently, both sets of authors considered an MTP of the form

$$d(a, w) = \begin{cases} a + \delta(w) & \text{if } a + \gamma \leq u(w) \\ a & \text{if } a + \gamma > u(w) \end{cases}, \text{where} \quad \delta(w) = \gamma \in \mathbb{R} \tag{1.1}$$

and $u(w)$ is the maximum value in the conditional support of $g_{0,A}(\cdot \mid W = w)$. This intervention generates a counterfactual random variable $Y_{d(A,W)} \coloneqq f_Y(d(A, W), W, U_Y)$ whose distribution we denote P_0^δ. The goal, then, is to estimate $\psi_{0,\delta} \coloneqq \mathbb{E}_{P_0^\delta}\{Y_{d(A,W)}\}$, the mean of this counterfactual outcome.

Identifying the Population Intervention Effect

Díaz and van der Laan [37] introduced the *population intervention effect* (PIE) $\theta_{0,\delta} \coloneqq \psi_{0,\delta} - \mathbb{E}Y$. As $\mathbb{E}Y$ is trivially estimable from the observed data, their efforts focused on identification and

estimation of $\psi_{0,\delta}$. In particular, these authors showed that $\psi_{0,\delta}$ is identified by

$$\begin{aligned}\psi_{0,\delta} &= \int_{\mathcal{W}} \int_{\mathcal{A}} \overline{Q}_{0,Y}(a,w) g_{0,A}(d^{-1}(a,w) \mid W = w) q_{0,W}(w) d\mu(a) d\nu(w) \\ &= \int_{\mathcal{W}} \int_{\mathcal{A}} \overline{Q}_{0,Y}(d(a,w),w) g_{0,A}(a \mid W = w) q_{0,W}(w) d\mu(a) d\nu(w) \end{aligned} \tag{1.2}$$

where $\overline{Q}_{0,Y}(a,w) := \mathbb{E}_{P_0}[Y \mid A = a, W = w]$, the conditional mean of Y given $A = a$ and $W = w$, as implied by P_0, and $g_{0,A}(a \mid W = w)$ is the conditional density of the treatment. For the statistical functional given in equation (1.2) to correspond to the causal estimand of interest, several untestable assumptions are required, including

A2 (Lack of interference)**.** Assume $Y_i^{d(a_i,w_i)} \perp\!\!\!\perp d(a_j, w_j)$ for $i \neq j$.

A3 (Consistency)**.** Assume $Y^{d(a,w)} = Y$ in the event $A = d(a,w)$.

A4 (No unmeasured confounding)**.** Assume $A \perp\!\!\!\perp Y^{d(a,w)} \mid W = w$.

A5 (Positivity)**.** Assume $a \in \mathcal{A} \implies d(a,w) \in \mathcal{A} \mid W = w$ for all $w \in \mathcal{W}$.

Together, assumptions A2 and A3 are often referred to as the stable unit treatment value assumption (SUTVA) [146, 148]. The positivity assumption A5, required to establish equation (1.2), is unlike its analog for simpler (i.e., static or dynamic) intervention schedules. Instead of requiring positive mass to be placed across all treatment levels for all covariate strata $w \in \mathcal{W}$, this positivity assumption requires only that the post-intervention treatment mechanism be bounded, i.e., $\mathbb{P}_{P_0}\{g_{0,A}(d^{-1}(A,W) \mid W)/g_{0,A}(A \mid W) > 0\} = 1$, which may generally be satisfied by a suitable choice of the parameter $\delta(W)$ in the treatment modification function $d(A,W)$.

Beyond their careful study of the identification of this causal effect, Díaz and van der Laan [37, 38] derived the *efficient influence function* (EIF), a quantity central to semiparametric efficiency theory, of $\psi_{0,\delta}$ with respect to the nonparametric statistical model $\mathcal{M}$. Using the EIF, these authors proposed efficient estimators constructed based on the form of the EIF. When evaluated on a typical observation o, a suitable expression for the EIF is

$$D^\star(P_0)(o) = H(a,w)\{y - \overline{Q}_{0,Y}(a,w)\} + \overline{Q}_{0,Y}(d(a,w),w) - \psi_{0,\delta}, \tag{1.3}$$

where the auxiliary covariate $H(a,w)$ takes the form $H(a,w) = g_{0,A}(d^{-1}(a,w) \mid w)/g_{0,A}(a \mid w)$. The EIF characterizes the best possible asymptotic variance, or efficiency bound, of all regular asymptotically linear estimators of $\psi_{0,\delta}$ and may thus be used in the development of efficient estimation strategies.

Estimating the Population Intervention Effect

To facilitate estimation of $\psi_{0,\delta}$, Díaz and van der Laan [38] defined a direct (or, substitution) estimator based on the G-computation formula. This classical estimator is of the form

$$\begin{aligned}\psi_{n,\delta}^{\text{SUB}} &:= \int \overline{Q}_{n,Y}(d(a,w),w)dQ_{n,AW}(a,w) \\ &= \frac{1}{n}\sum_{i=1}^{n}\overline{Q}_{n,Y}(d(A_i,W_i),W_i)\ , \end{aligned} \tag{1.4}$$

where $Q_{n,AW}(a,w)$ is an estimate of the joint distribution of (A,W) based on the empirical distribution. An inverse probability weighted (IPW) estimator of $\psi_{0,\delta}$ takes the form

$$\psi_{n,\delta}^{\text{IPW}} = \frac{1}{n}\sum_{i=1}^{n}\frac{g_{n,A}(d^{-1}(A_i,W_i)\mid W_i)}{g_{n,A}(A_i\mid W_i)}Y_i\ . \tag{1.5}$$

In both equations (1.4) and (1.5), as well as in the sequel, the subscript n denotes the use of estimated quantities in lieu of their true counterparts — that is, $g_{n,A}$ is simply an estimate of the conditional treatment density $g_{0,A}$, while $\overline{Q}_{n,Y}$ is an estimate of the outcome mechanism $\overline{Q}_{0,Y}$. Both the direct estimator $\psi_{n,\delta}^{\text{SUB}}$ and the IPW estimator $\psi_{n,\delta}^{\text{IPW}}$ require estimation of only a single nuisance parameter (the outcome mechanism and the conditional treatment density, respectively) but are well-known to be irregular, fail to be asymptotically consistent, or fail to achieve the semiparametric efficiency bound. What's more, neither estimator is asymptotically linear for $\psi_{0,\delta}$ when flexible regression strategies are used for nuisance parameter estimation, significantly limiting the scenarios in which these approaches may be successfully applied.

Two popular frameworks for efficient estimation, both taking advantage of the EIF, include one-step estimation [127, 14] and targeted minimum loss-based (TML) estimation [180, 179, 178]. Importantly, both the one-step and TML estimators are *doubly robust*, a property which affords two important conveniences. Firstly, both estimators are consistent for $\psi_{0,\delta}$ when either of the initial estimates of $g_{n,A}$ and $\overline{Q}_{n,Y}$ are consistent for their respective targets; however, these estimators only achieve asymptotic efficiency when *both* initial estimates are consistent. Secondly, as a consequence of their explicit construction based on the EIF, both readily accommodate the use of flexible, data-adaptive estimation strategies for the initial estimation of nuisance parameters. This latter property provides these estimators with a distinct advantage over their substitution and IPW estimator counterparts: two opportunities to avoid model misspecification from restrictive (e.g., parametric) modeling strategies.

Invoking either estimation strategy proceeds first by constructing initial estimates, $g_{n,A}$ and $\overline{Q}_{n,Y}$, of the conditional treatment density $g_{0,A}$ and the outcome mechanism $\overline{Q}_{0,Y}$. The two approaches diverge at their second stage, which focuses on bias correction. In the one-step frame-

work, this amounts to updating the initial substitution-based estimate $\psi_{n,\delta}$ by adding to it the empirical mean of the estimated EIF. In the TML estimation framework, a univariate (often, logistic) parametric tilting model is used to update the initial estimate $\overline{Q}_{n,Y}$ of the outcome mechanism in such a way that the EIF estimating equation is solved to a desirable degree. Plugging this updated initial estimate into the substitution formula given in equation (1.4) results in a targeted estimator of $\psi_{0,\delta}$.

As both the one-step and TML estimation procedures require the EIF, we recall that an estimate of the EIF may be constructed from equation (1.3) by plugging in initial estimates of nuisance parameters. The estimated EIF, evaluated on observation i, is

$$D^{\star}_{n,i} \coloneqq H_n(A_i, W_i)\{Y_i - \overline{Q}_{n,Y}(A_i, W_i)\} + \overline{Q}_{n,Y}(d(A_i, W_i), W_i) - \psi_{n,\delta}$$

with auxiliary term $H_n(a, w) \coloneqq g_{n,A}(d^{-1}(a, w) \mid w)/g_{n,A}(a \mid w)$. Using the estimated EIF $D^{\star}_{n,i}$, the one-step estimator may then be defined

$$\psi^{+}_{n,\delta} \coloneqq \psi_{n,\delta} + \frac{1}{n}\sum_{i=1}^{n} D^{\star}_{n,i} \,. \tag{1.6}$$

Similarly, an asymptotically linear TML estimator may be constructed by updating the initial estimator $\overline{Q}_{n,Y}$ to a tilted variant $\overline{Q}^{\star}_{n,Y}$, through a logistic tilting model of the form $\operatorname{logit} \overline{Q}^{\star}_{n,Y} = \operatorname{logit} \overline{Q}_{n,Y} + \epsilon H_n$, in which the initial estimate $\overline{Q}_{n,Y}$ is taken as an offset and only the parameter ϵ need be estimated. The targeted plug-in estimator is then

$$\psi^{\star}_{n,\delta} \coloneqq \int \overline{Q}^{\star}_{n,Y}(d(a, w), w) dQ_{n,AW}(a, w) \,. \tag{1.7}$$

Both of these efficient estimators depend on initial estimates of the nuisance functions $(\overline{Q}_{n,Y}, g_{n,A})$. Throughout, we focus on developing improved estimators $g_{n,A}$ of the generalized propensity score $g_{0,A}$, ultimately towards the goal of facilitating the construction of enhanced efficient estimators of $\psi_{0,\delta}$.

The Highly Adaptive Lasso Estimator

In our subsequent developments, we make use of a recently developed nonparametric regression function, the highly adaptive lasso (HAL) [167, 170]. The HAL estimator approximates a functional parameter of interest using a linear combination of basis functions, with the requirement that the target functional parameter belong to the set of càdlàg (i.e., right-hand continuous with left-hand limits) functions with sectional variation norm bounded by a finite (but unknown) constant, a global smoothness restriction that limits the degree of variability that the target functional may

exhibit. Similarly positioned approaches in nonparametric estimation generally require more restrictive local smoothness assumptions. For example, minimax convergence rates achieved under the assumption that the target functional belongs to a smoothness class characterized by Hölder balls [e.g., 135, 142] are compromised by the failure of resultant function classes to exclude from admissibility highly erratic functions (e.g., the Weierstrass function, which falls in the class of Hölder-α functions for $\alpha < 1$ and $d = 1$).

For any function $f \in \mathcal{D}[0, \tau]$, the Banach space of d-variate real-valued càdlàg functions on a cube $[0, \tau] \in \mathbb{R}^d$, the sectional variation norm of f may be expressed

$$\|f\|_\nu^\star \coloneqq |f(0)| + \sum_{s \subset \{1,\ldots,d\}} \int_{0_s}^{\tau_s} |df_s(u_s)|,$$

where s are subsets of $\{0, 1, \ldots, d\}$, defined by partitioning $[0, \tau]$ in $\{0\}\{\cup_s(0_s, \tau_s]\}$, and the sum is taken over all subsets of the coordinates $\{0, 1, \ldots, d\}$. For a given subset $s \subset \{0, 1, \ldots, d\}$, define $u_s = (u_j : j \in s)$ and u_{-s} as the complement of u_s; then, $f_s : [0_s, \tau_s] \to \mathbb{R}$, defined as $f_s(u_s) = f(u_s, 0_{-s})$. Thus, $f_s(u_s)$ is a section of f that sets the components in the complement of s to zero, that is, allowing variation only along components in u_s.

van der Laan [166, 167] proved that the HAL estimator converges to the target functional at a rate faster than $n^{-1/4}$, without any contribution from the dimensionality d of the problem at hand, so long as d remains fixed. Subsequent theoretical investigations improved this rate of convergence to $n^{-1/3} \log(n)^{d/2}$ [13], with ongoing work yielding promising further improvements still. The HAL estimator can be thought of as proceeding in two general steps. Firstly, a rich set of indicator (or higher-order, i.e., spline) basis functions are generated to represent the target functional; this step is a mapping of the covariate space in terms of the HAL basis. Subsequently, lasso regression [163] is applied to a linear combination of these basis functions, minimizing the expected value of an appropriately chosen loss function while constraining the L_1-norm of the vector of coefficients to be bounded by a finite constant matching the sectional variation norm of the HAL representation of the target functional. Benkeser and van der Laan [11] first demonstrated the utility of the HAL estimator in an extensive series of numerical experiments. The HAL estimator is implemented in the free and open source `hal9001` package [30, 75] for the `R` language and environment for statistical computing [133].

When a nuisance parameter of interest is taken as the target functional, the HAL estimator may be applied to generate initial estimates, under the assumption that the true nuisance parameter functional (e.g., the generalized propensity score) be of finite sectional variation. When the nuisance

parameter η, with arbitrary input Z, is real-valued, its HAL representation may be expressed

$$\begin{aligned}\eta(z) &= \eta(0) + \sum_{s \subset \{1,\ldots,d\}} \int_{0_s}^{z_s} d\eta_s(u_s) \\ &= \eta(0) + \sum_{s \subset \{1,\ldots,d\}} \int_{0_s}^{\tau_s} \mathbb{I}(u_s \leq z_s) d\eta_s(u_s), \end{aligned} \tag{1.8}$$

which can be approximated by the use of a discrete measure placing mass on each observed $Z_{s,i}$. When the range of η is the unit interval, an analogous approach, using instead $\operatorname{logit} \eta$, may be pursued based on a representation of Gill, van der Laan, and Wellner [62]; Ertefaie, Hejazi, and van der Laan [48] work with this representation in using HAL regression for estimation of the propensity score for binary treatments. Now, take $z_{s,i}$ to be support points of η_s and let $\phi_{s,i}(c_s) \coloneqq \mathbb{I}(z_{s,i} \leq c_s)$, then

$$\eta_\beta = \beta_0 + \sum_{s \subset \{1,\ldots,d\}} \sum_{i=1}^{n} \beta_{s,i} \phi_{s,i},$$

where $|\beta_0| + \sum_{s \subset \{1,\ldots,d\}} \sum_{i=1}^{n} |\beta_{s,i}|$ is an approximation of the sectional variation norm of η. The loss-based HAL estimator β_n may then be defined

$$\beta_{n,\lambda} = \underset{\beta : |\beta_0| + \sum_{s \subset \{1,\ldots,d\}} \sum_{i=1}^{n} |\beta_{s,i}| < \lambda}{\operatorname{argmin}} P_n L(\eta_\beta),$$

where $P_n f = n^{-1} \sum_{i=1}^{n} f(O_i)$ and $L(\cdot)$ is an appropriately chosen loss function; see Dudoit and van der Laan [45] for an illuminating discussion of appropriate choices of loss function for a range of loss-based estimation problems. Salient to our goal of estimating the generalized propensity score, the negative log-likelihood loss, $L(\eta) = -\log(p_\eta)$, is a suitable loss function for density estimation. Finally, the HAL estimate of η may be denoted $\eta_{n,\lambda} \equiv \eta_{\beta_{n,\lambda}}$. Each choice of the regularization term λ corresponds to a unique HAL estimator, though, generally speaking, methods for the selection of λ must be tailored to the estimation goal in order to yield suitable candidate estimators.

1.3 Estimating the Generalized Propensity Score

We now turn to procedures for estimation of the generalized propensity score $g_{0,A}$, from which we may be able to subsequently develop efficient, nonparametric estimators of $\psi_{0,\delta}$. As will be demonstrated in the sequel, both conditional density estimators are flexible, allowing for the use of arbitrary, data-adaptive regression methods to be leveraged. For compatibility with our subsequent theoretical results, we present our conditional density estimation procedures using the HAL

estimator discussed in Section 1.2; this is chiefly for three reasons. Firstly, formal theory guarantees a suitable convergence rate, for estimator construction, when the HAL estimator is used to approximate a nuisance functionals. Secondly, contemporaneous efforts have made headway in developing efficient direct and IPW estimators of low-dimensional parameters in causal inference settings [168, 48]. Thirdly, the algorithm is readily available in the free and open source `hal9001` `R` package [30, 75].

In considering estimation of $g_{0,A}$, a straightforward strategy involves assuming a parametric working model for relevant moments of the density function, allowing the use of standard regression techniques to generate suitable estimates [138, 81, 88]. For example, one could operate under the working assumption that the density of A given W follows a Gaussian distribution with homoscedastic variance and mean $\sum_{j=1}^{p} \beta_j \phi_j(W)$, where $\phi = (\phi_j : j)$ are user-specified basis functions and $\beta = (\beta_j : j)$ are unknown regression parameters. Under such a regime, a density estimate could be generated by fitting a linear regression of A on $\phi(W)$ to estimate $\mathbb{E}[A \mid W]$, paired with maximum likelihood estimation of the variance of A. In this case, the estimated conditional density would be given by the density of a Gaussian distribution evaluated at these estimates. While a reasonable approach, such a strategy makes strong parametric assumptions about the form of the conditional density function and may, on this account, be more prone to model misspecification than alternative strategies that make fewer such assumptions.

Constructing a flexible density estimator is a more challenging problem, as the set of available tools is considerably limited. These limitations motivated our investigations of novel conditional density estimators capable of incorporating arbitrary regression functions. We describe two such classes of estimators in the sequel, with implementations of these proposals provided in the free and open source `sl3` and `haldensify` `R` packages [31, 74], respectively.

Semiparametric Location-Scale Estimators

A recently developed family of flexible semiparametric conditional density estimators takes the general form $\rho(A - \mu(W)/\sigma(W))$, where ρ is a given marginal density function. Conditional density estimation procedures falling within this framework may be characterized as belonging to a *conditional location-scale* family, i.e., where $g_{n,A}(A \mid W) = \rho((A - \mu_n(W))/\sigma_n(W))$; where we stress that the marginal density mapping ρ is selected *a priori*, leaving only the relevant moments μ and σ to be estimated.

Though the restriction to (conditional) location-scale families imposes some limitations on the form of the target functional, the strategy is made particularly flexible by its ability to incorporate arbitrary, data-adaptive regression strategies for the estimation of $\mu(W) = \mathbb{E}[A \mid W]$ and, optionally, of the conditional variance $\sigma(W) = \mathbb{E}[(A - \mu(W))^2 \mid W]$. In particular, in settings with

limited data, the additional structure imposed by the assumption of form of the target density functional (i.e., in the specified kernel function ρ) can prove beneficial, when the true density function admits such a representation. While we stress that this procedure is surely not a novel contribution of the present work, we have been otherwise unable to ascertain a formal description of it; thus, we provide such a formalization in Algorithm 1, which sketches the construction of conditional density estimators of this family.

Algorithm 1: Location-scale conditional density estimation

Result: Estimates of the conditional density of A, given W.

Input :

An observed data vector of the continuous treatment for n units: A

An observed data vector (or matrix) of the baseline covariates for n units: W

A kernel function specification to be used to construct the density estimate: ρ

A candidate regression procedure to estimate the conditional mean $\mu(W)$: f_μ

A candidate regression procedure to estimate the conditional variance $\sigma(W)$: f_σ

1. Estimate $\mathbb{E}[A \mid W]$, the conditional mean of A given W, by applying the regression estimator f_μ, yielding $\hat{\mu}(W)$.
2. Estimate $\mathbb{V}[A \mid W]$, the conditional variance of A given W, by applying the regression estimator f_σ, yielding $\hat{\sigma}^2(W)$. Note that this step involves only estimation of the conditional mean $\mathbb{E}[(A - \hat{\mu}(W))^2 \mid W]$.
3. Estimate the one-dimensional density of $(A - \hat{\mu}(W))^2 / \hat{\sigma}^2(W)$, using kernel smoothing to obtain $\hat{\rho}(A)$.
4. Construct the estimated conditional density $g_{n,A}(A \mid W) = \hat{\rho}((A - \hat{\mu}(W))/\hat{\sigma}(W))$.

Output: $g_{n,A}$, an estimate of the generalized propensity score.

The sketch of the algorithm for constructing estimators $g_{n,A}(a \mid w)$ of the generalized propensity score may take two forms, which diverge at the second step above. Firstly, one may elect to estimate only the conditional mean $\mu(W)$ via a regression technique, leaving the variance to be taken as constant (estimated simply as the marginal mean of $\mathbb{E}[(A - \hat{\mu}(W))^2]$). Estimators of this form may be described as having *homoscedastic error*, based on the variance assumption made.

Alternatively, one may additionally estimate the conditional variance $\sigma^2(W)$ via the residuals of the estimated conditional mean, that is, estimating instead the conditional mean $\mathbb{E}[(A - \hat{\mu}(W))^2 \mid W]$.

While the regression procedures f_μ and f_σ used to estimate the conditional mean $\mu(W)$ and the conditional variance $\sigma^2(W)$, respectively, may be arbitrary, with candidates including, for example, random forests [16], spline regression [157, 55], or regression ensembles [193, 17, 176], we recommend the use of HAL regression [11, 167], as its use will ensure an enhanced rate of convergence [13] of the estimator $g_{n,A}$ to its target $g_{0,A}$. The data-adaptive nature of HAL regression affords a degree of flexibility that ought to limit opportunities for model misspecification to compromise estimation of $g_{0,A}$; morever, their improved convergence rate will help to facilitate the construction of asymptotically linear, and possibly efficient, estimators of $\psi_{0,\delta}$.

Nonparametric Hazard Regression Estimator

Estimators that eschew any assumptions on the form of the conditional density are a rarity. Notably, Díaz and van der Laan [39] gave a proposal for constructing semiparametric estimators of this target quantity based on exploitation of the relationship between the (conditional) hazard and density functions. Our proposal builds upon theirs, replacing the original recommendation of an arbitrary classification model with the HAL regression function. This contribution requires the key change of adjusting the penalization aspect of HAL regression to respect the use of a loss function appropriate for prediction on the hazard scale, i.e., $-\log g_{n,A}$ [45]. As a consequence of this adjustment, the resultant conditional density estimator is made capable of incorporating sample-level weights.

To build an estimator of a conditional density, Díaz and van der Laan [39] considered discretizing the observed $A \in \mathcal{A}$ based on a number of bins T and a binning procedure (e.g., equally distributing observed mass across each of the T bins or forcing each of the T bins to be of the same length). The choice of the tuning parameter T corresponds conceptually to the choice of bandwidth in classical kernel density estimation. To take an example, an instantiation of this procedure would divide the observed support of A into, say, $T = 7$, bins of equal length. Such a partitioning would require $T + 1$ cutpoints along the support of A, yielding T bins: $[\alpha_1, \alpha_2), [\alpha_2, \alpha_3), \ldots, [\alpha_6, \alpha_7), [\alpha_7, \alpha_8]$. Next, relevant components of the observed data $\{A_i, W_i\}_{i=1}^n$ would be reformatted such that each observational unit $\{A_i, W_i\}$ would be represented by a set of up to T records, with the number of records for a given unit matching the position of the bin into which the observed A_i falls. For clarity, consider an individual unit $\{A_i, W_i\}$ for which the value A_i falls in the fifth bin of the seven into which the support has been partitioned (i.e., $[\alpha_5, \alpha_6)$). Five distinct records would be used to represent the data on this single unit: $\{A_{ij}, W_{ij}\}_{j=1}^5$, where $\{\{A_{ij} = 0\}_{j=1}^4, A_{i5} = 1\}$ and five exact copies of W_i, $\{W_{ij}\}_{j=1}^5$. This representation as multiple

records allows for the hazard probability of A_i belonging to a particular bin along the discretized support to be evaluated via standard classification techniques. In fact, this proposal reformulates the classification problem into a corresponding set of hazard regressions:

$$\begin{aligned}\mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid W) =& \mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid A \geq \alpha_{t-1}, W) \\ & \times \prod_{j=1}^{t-1} \{1 - \mathbb{P}(A \in [\alpha_{j-1}, \alpha_j) \mid A \geq \alpha_{j-1}, W)\},\end{aligned}$$

where the probability of $A \in \mathcal{A}$ falling in a bin $[\alpha_{t-1}, \alpha_t)$ may be directly estimated from any arbitrary binary regression model, since the likelihood of this model may be re-expressed in terms of the likelihood of a binary variable in a data set expressed through a repeated measures structure.

Specifically, this data-reformatting procedure is carried out by creating a data set in which any given observation A_i appears (repeatedly) for as many intervals $[\alpha_{t-1}, \alpha_t)$ as there are prior to the interval to which the observed a belongs. A new binary outcome variable, indicating membership in the support set, is generated and recorded as part of this new data structure. With the reformatted data, a pooled hazard regression, spanning the support of A is then performed. Finally, the conditional density estimate may be constructed as

$$g_{n,\alpha}(A \mid W) = \frac{\mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid W)}{|\alpha_t - \alpha_{t-1}|} \, .$$

As part of this procedure, the hazard estimates are mapped to density estimates through re-scaling of the estimates by the bin size $|\alpha_t - \alpha_{t-1}|$. We formalize this procedure in Algorithm 2.

Algorithm 2: Pooled hazard conditional density estimation

Result: Estimates of the conditional density of A, given W.

Input :

An observed data vector of the continuous treatment for n units: A

An observed data vector (or matrix) of the baseline covariates for n units: W

A scalar indicating the number of bins into which the support of A is to be divided: T

A procedure for discretizing the support of A into the selected number of bins T: ω

1. Apply the procedure $\omega(A, T)$ to divide the observed support of A into T bins: $[\alpha_1, \alpha_2), \ldots, [\alpha_{T-1}, \alpha_T), [\alpha_T, \alpha_{T+1}]$.
2. Expand the observed data in a repeated measures data structure, expressing each individual observation as a set of up to T records, recording the observation ID alongside each such record. For a single unit i, the set of records takes the form $\{A_{ij}, W_{ij}\}_{j=1}^{T_i}$, where W_{ij} are constant in the index j, A_{ij} is a binary counting process that jumps from 0 to 1 at the final index, and $T_i \leq T$ indicates the bin along its support into which A_i falls.
3. Estimate the hazard probability, conditional on W, of bin membership $\mathbb{P}(A_i \in [\alpha_{t-1}, \alpha_t) \mid W)$ using HAL regression, using cross-validation to choose the regularization parameter based on a loss function for density estimation, e.g., the negative logarithm of the estimated density [45].
4. Rescale the conditional hazard probability estimates to the conditional density scale by dividing the cumulative hazard by the width of the bin into which A_i falls, for each observation $i = 1, \ldots, n$.

Output: $g_{n,A}$, an estimate of the generalized propensity score.

In its original proposal, a key element of this procedure was the use of any arbitrary binary regression procedure to estimate $\mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid W)$, facilitating the incorporation of flexible, data adaptive estimators [39]. We alter this proposal, replacing the arbitrary estimator of $\mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid W)$ with HAL regression, making it possible for the resultant conditional density estimator to achieve a convergence rate with respect to a loss-based dissimilarity of $n^{-1/3}$ under only mild assumptions [167, 170]. We stress that this is an important advance that is needed for the asymptotic analysis of estimators of $\psi_{0,\delta}$.

Nonparametric Inverse Probability Weighted Estimation

We now turn our attention to considering estimators of $\psi_{0,\delta}$ that can be constructed solely from nuisance estimation of the generalized propensity score $g_{0,A}$. It is well-known that data adaptive estimators of nuisance functionals are generally incompatible with the direct (i.e., G-computation) and IPW estimators, as necessary conditions for achieving asymptotic desiderata (e.g., consistency, efficiency) are unattainable without the imposition of strong smoothness assumptions on the functional form of the nuisance parameter estimator. This theoretical impasse has, in part, fueled the now-considerable popularity enjoyed by doubly robust estimation procedures, such as those constructed within the one-step estimation [14] or targeted minimum loss-based estimation frameworks [180, 179, 178]. As noted previously, we recall that doubly robust estimators require estimation of both the outcome mechanism $\overline{Q}_{0,Y}$ and the propensity score $g_{0,A}$; moreover, such estimators are consistent for $\psi_{0,\delta}$ when either of the two nuisance parameter estimators converge to their targets but asymptotically efficient only when *both* nuisance estimators converge. In settings wherein consistent estimation of the outcome mechanism $\overline{Q}_{0,Y}$ can prove challenging, asymptotic efficiency may yet be attained by focusing on a unique class of IPW estimators capable of incorporating data adaptive estimation of $g_{0,A}$ while achieving asymptotic efficiency. The construction of such IPW estimators requires considerable care and has been considered previously by Hirano, Imbens, and Ridder [82], who proposed a logistic series estimator of the propensity score, requiring strong smoothness assumptions, and, more recently, by Ertefaie, Hejazi, and van der Laan [48], who propose the use of HAL regression.

To construct nonparametric-efficient IPW estimators, we utilize the generalized propensity score estimator described in Algorithm 2, which makes use of HAL regression for estimation of the conditional hazard, and build upon the recent theoretical developments of Ertefaie, Hejazi, and van der Laan [48], who demonstrated that the application of an undersmoothing procedure to select a HAL estimator of the propensity score could yield an IPW estimator that achieves the nonparametric efficiency bound. Notably, the developments of these authors were restricted to IPW estimation of the causal effects of static interventions on binary (or categorical) treatments (e.g., average treatment effects), requiring only consistent estimation of the standard propensity score [144] $g_{0,A} = \mathbb{P}(A = 1 \mid W)$, that is, the conditional probability of receiving treatment given covariates. Ertefaie, Hejazi, and van der Laan [48] provide general conditions under which HAL regression may be used to obtain a data adaptive estimator $g_{n,A}$ that converges to $g_{0,A}$ at a suitably fast rate. Further, these authors showed that their nonparametric IPW estimators could be asymptotically efficient when the HAL estimator $g_{n,A}$ is undersmoothed (relative to the estimator selected by V-fold cross-validation) so as to include a larger number of basis functions than is required for optimal estimation of $g_{0,A}$.

We propose two classes of selection procedures for undersmoothing HAL estimators of the generalized propensity score, both beginning with a common first step: construction of a family of HAL-based conditional density estimators indexed by the regularization parameter λ. For this step, we recommend merely an application of Algorithm 2, altering the procedure so as to omit the use of cross-validation to choose the regularization parameter λ; thus, rather than a single estimator $g_{n,A}$, the algorithm is made to return a family of estimators $\{g_{n,A,\lambda} : \lambda_1, \ldots, \lambda_K\}$. We recommend the family of nonparametric estimators described by Algorithm 2 for the very high degree of flexibility offered; however, the semiparametric location-scale conditional density estimators outlined in Algorithm 1 can just as easily be adapted for this purpose, with similarly minor adjustments. We assume access to a grid of generalized propensity score estimators $\{g_{n,A,\lambda} : \lambda_1, \ldots, \lambda_K\}$, for $\lambda_1 > \ldots > \lambda_K$, facilitating the construction of a grid of IPW estimators $\{\psi_{n,\delta,\lambda} : \lambda_1, \ldots, \lambda_K\}$, similarly indexed by $\{\lambda_1, \ldots \lambda_K\}$. What remains then is to select a single IPW estimator that exhibits desirable asymptotic properties from this set of candidates.

In considering the same goal, Ertefaie, Hejazi, and van der Laan [48] propose two types of undersmoothing criteria: (1) minimization of the mean of the efficient influence function up to a desirable degree, and (2) minimization of a score term arising from the treatment mechanism $(A - g_{n,A})$. Their first selector makes explicit use of the form of the EIF and must thus be derived anew for any given intervention regime. As a minor contribution, we provide the first explicit re-characterization of the EIF of equation (1.3) in a form suitable for IPW estimator selection. The second selection procedure is incompatible with stochastic interventions, as there is no explicit score for the treatment mechanism in this setting. Intuitively, this is attributable to the fact that the stochastic intervention $d(A, W)$ defined by equation (1.1) depends on the natural value of the treatment A, not the case in static or dynamic treatment regimes. Alternatively, we develop a novel class of selection procedures based on changes in the IPW estimators $\{\psi_{n,\delta,\lambda} : \lambda_1, \ldots, \lambda_K\}$ as the regularization parameter λ is weakened. Importantly, we note that, as an integral aspect of both of these contributions, we provide, to or knowledge, the first demonstration of the undersmoothing of conditional density estimators.

Targeted Undersmoothing, with the Influence Function

In order to select an IPW estimator from the grid $\{\psi_{n,\delta,\lambda} : \lambda_1, \ldots, \lambda_K\}$ based on the EIF, it is necessary to re-express the EIF in a form incorporating the IPW estimating function, which can be done via projection of this latter object onto the space of all functions of A that are mean-zero conditional on W [141, 177]. In this direction, our developments follow closely those of Ertefaie, Hejazi, and van der Laan [48]. To proceed, we note that the stabilized IPW estimator, a minor

adaptation of the estimator of equation 1.5, is

$$\psi_{n,\delta}^{\text{IPW}} = \frac{1}{n}\sum_{i=1}^{n} \frac{\{g_{n,A}(d^{-1}(A_i, W_i) \mid W_i)/g_{n,A}(A_i \mid W_i)\}}{\frac{1}{n}\sum_{i=1}^{n}\{g_{n,A}(d^{-1}(A_i, W_i) \mid W_i)/g_{n,A}(A_i \mid W_i)\}} Y_i. \tag{1.9}$$

The inverse probability weighted mapping defining the estimating function of this estimator takes the form:

$$U_{g_A}(O; \Psi)(P) = \frac{g_{n,A}(d^{-1}(A, W) \mid W)}{g_{n,A}(A \mid W)}(Y - \Psi(P)). \tag{1.10}$$

Note that the IPW estimator appearing in equation 1.9 is simply a solution to the estimating function given in equation 1.10. We now present Lemma 1, which explicitly characterizes the required form of the EIF.

Lemma 1 (IPW representation of the EIF)**.** *Let $D^\star(P)$ denote the EIF (equation 2.2) and let $U_{g_A}(\Psi)$ denote the IPW estimating function (equation 1.10). Then, the projection of $U_{g_A}(\Psi)$ onto T_{CAR}, the tangent space of all functions of A that are mean-zero, conditional on W, yields $D^\star(P) = U_{g_A}(\Psi)(P) - D_{CAR}(P)$, where the latter term is of the form*

$$D_{CAR}(P_0) = \left[Q_{0,Y}(d(A, W), W) - \left(\frac{g_{0,A}(d^{-1}(A, W) \mid W)}{g_{0,A}(A \mid W)}\right) Q_{0,Y}(A, W)\right] - \Psi(P_0) \cdot \left(\frac{g_{0,A}(A \mid W) - g_{0,A}(d^{-1}(A, W) \mid W)}{g_{0,A}(A \mid W)}\right).$$

Given a family of IPW estimators $\{\psi_{n,\delta,\lambda} : \lambda_1, \ldots, \lambda_K\}$, an optimal IPW estimator may be selected based on minimization (up to a tolerance τ) of $|P_n D_{CAR}|$, the empirical mean of the estimate, evaluated at the nuisance parameter estimates $\{g_{n,A}, Q_{n,Y}\}$. The selected estimator $\psi_{n,\delta,\lambda}$ is an approximate solution to the estimated EIF.

As noted in Lemma 1, the term D_{CAR} arises by projection of the estimating function $U_{g_A}(\Psi)$ onto the tangent space $T_{\text{CAR}} = \{\zeta(A, W) : \mathbb{E}_{P_0}\{\zeta(A, W) \mid W\} = 0\}$ [141, 177]. Intuitively, since IPW estimators are constructed as explicit solutions to the empirical mean of $U_{g_A}(O; \Psi)$, the first term of the EIF representation in the lemma is trivially solved; thus, selection of an IPW estimator need only consider the second term. Our selector is then

$$\lambda_n = \underset{\lambda}{\text{argmin}} |P_n D_{\text{CAR}}(g_{n,A,\lambda}, Q_{n,Y})|.$$

Agnostic Undersmoothing, without the Influence Function

As demonstrated in the preceding section, explicit characterization of the form of the EIF in a manner amenable to the selection of an IPW estimator can prove a challenging endeavor, requiring

specialized and often-tedious mathematical manipulations. In many cases, it may serve to select an IPW estimator in a manner that eschews such complications. A procedure that does not make use of the EIF has the additional advantage of remaining applicable across a wide range of intervention regimes, allowing for its use in a possibly vast array of settings, without the need for either re-derivation or re-implementation. Towards this end, we formulate two selection procedures that do not make use of the form of the EIF at all, instead considering properties of the IPW estimators $\{\psi_{n,\delta,\lambda} : \lambda_1, \ldots, \lambda_K\}$ along the trajectory that emerges with respect to the regularization grid $\lambda_1, \ldots, \lambda_K$. In the larger context of general nonparametric estimation and sieve methods, such ideas were popularized in seminal work by Lepskii [101, 100], with extensions appearing sporadically in the literature [e.g., 102, 15].

The formulation of such EIF-agnostic selection procedures for undersmoothing aims to produce selections similar to those given by the targeted procedures — that is, while the agnostic selectors do no explicitly use the form of the EIF, their selections must still solve the EIF in order to asymptotically attain the nonparametric efficiency bound. Our first proposal in this class balances changes along the regularization sequence $\{\lambda_1, \ldots, \lambda_K\}$,in the IPW estimator $\psi_{n,\delta,\lambda}$ against changes in its estimated variance $\sigma_{n,\lambda}$. This selection λ_n is merely the first element of $\lambda_1, \ldots, \lambda_K$ for which the condition

$$|\psi_{n,\delta,\lambda_{j+1}} - \psi_{n,\delta,\lambda_j}|_{j=1}^{K-1} \leq Z_{(1-\alpha/2)}[\sigma_{n,\lambda_{j+1}} - \sigma_{n,\lambda_j}]_{j=1}^{K-1} \tag{1.11}$$

is met. Note that $Z_{(1-\alpha/2)}$ is the $(1-\alpha/2)^{\text{th}}$ quantile of the standard normal distribution, useful for the construction of Wald-style confidence intervals. While we recommend the use of the stabilized IPW estimator of equation (1.9) in the criterion, there are several choice of the standard error estimate $\sigma_{n,\lambda}$. For ease of computation, we recommend a well-known, conservative variance estimator, the empirical variance of the estimated IPW estimating equation $\mathbb{V}\{U_{g_{n,A}}(\psi_{n,\delta,\lambda})\}/n$. When computational limitations are not of concern, one might instead consider the bootstrap estimate of the variance, which has been shown to be compatible with HAL-based nuisance estimation [22]. Upon examination of its form, it is revealed that the proposed selector identifies λ_n as the first point in $\lambda_1, \ldots, \lambda_K$ that changes in the IPW point estimates are less than changes in the corresponding variance estimates, with the latter scaled by the scalar $Z_{(1-\alpha/2)}$. Intuitively, satisfaction of this criterion conincides with relaxing of the regularization parameter impacting the variance estimate moreso than it does the IPW point estimate, thus indicating that a desirable bias-variance tradeoff has been achieved for the IPW estimator.

A potential pitfall of the immediately preceding proposal is its requirement of variance estimation, which can be computationally challenging (e.g., requiring the bootstrap), result in unstable estimates, or require nuisance estimation beyond $g_{0,A}$. It is possible to eschew variance estimation altogether, relying instead entirely on the trajectory of $\{\psi_{n,\delta,\lambda} : \lambda_1, \ldots, \lambda_K\}$ alone. The selection

λ_n is simply the first in $\lambda_1, \ldots, \lambda_K$ where the following is satisfied

$$\left[\frac{|\psi_{n,\delta,\lambda_{j+1}} - \psi_{n,\delta,\lambda_j}|}{\max_j |\psi_{n,\delta,\lambda_{j+1}} - \psi_{n,\delta,\lambda_j}|}\right]_{j=1}^{K-1} \leq \tau \tag{1.12}$$

for an arbitrary tolerance level τ. Intuitively, this selection procedure considers the sharpness of changes in the point estimates $\psi_{n,\delta,\lambda}$ sequentially in the indices $\{\lambda_1, \ldots, \lambda_K\}$, as the degree of regularization is relaxed. The selector aims to identify a value λ_n at which changes in the point estimate $\psi_{n,\delta,\lambda_n}$ are dwarfed by the relative size of changes encountered thus far in the index λ. Equivalently, this selector can be thought of as identifying plateaus in the solution path of $\psi_{n,\delta,\lambda}$ in λ. We conjecture that an IPW estimator identified by this criterion will suitably solve the EIF estimating equation and thus achieve desirable asymptotic properties.

1.4 Numerical Studies

To examine numerically the performance of our proposed IPW estimators, we considered a set of simulation studies across three distinct data-generating processes (DGPs). Each of the DGPs was constructed to tease apart how differences in the form of the treatment mechanism $g_{0,A}$ may impact the relative performance of our proposed IPW estimators. The goal of our numerical experiments was to reveal scenarios, based on characteristics of $g_{0,A}$, in which one of our proposed IPW estimators ought to be preferred over another — consequently, we do not compare our proposed IPW estimators to the doubly robust estimators of $\psi_{0,\delta}$ previously described in Section 1.2. Throughout the experiments, we illustrate that undersmoothing of our proposed IPW estimators can result in unbiased and efficient estimators of $\psi_{0,\delta}$, when $g_{0,A}$ is estimated using the conditional density estimator of Algorithm 2. Both the estimator of Algorithm 2 and our nonparametric IPW estimators of $\psi_{0,\delta}$ are implemented in the `haldensify` `R` package [74].

Throughout our experiments, we compare several variants of our IPW estimators $\psi_{n,\delta,\lambda_n}$, each differing in the manner in which the regularization parameter λ_n is selected. We consider a total of six variants: one in which cross-validation dictates the choice of λ_n (as per Algorithm 2); two based on the targeted undersmoothing criterion described in Lemma 1, choosing λ_n as the minimizer of $|P_n D_{\text{CAR}}|$ or through a relaxed condition under which $|P_n D_{\text{CAR}}|$ is required to only fall below a rescaling of a standard error estimate based on the EIF $\sqrt{\mathbb{V}(D_n^\star)/n}/\log(n)$; one based on the agnostic undersmoothing criterion of equation (1.11); and two based on the agnostic undersmoothing criterion of equation (1.12), where the cutoff τ is taken to be extreme $\tau = 0.01$ or relaxed $\tau = 0.2$.

Across each of three DGPs, we consider a collection of observed data units $O = (W_1, W_2, W_3, A, Y)$, where $W_1 \sim$ Bernoulli$(p = 0.6)$, $W_2 \sim$ Uniform$(\min = 0.5, \max = 1.5)$, and $W_3 \sim$ Poisson$(\lambda = 2)$; the generating functions for A and Y vary across the three scenarios. For each simulation experiment in a given scenario, we sample $n \in \{100, 200, 500\}$ units and apply the variants of our proposed IPW estimators to estimate $\psi_{0,\delta}$ at $\delta = 1$, repeating each experiment 300 times. We approximate $\psi_{0,\delta}$ in each scenario by applying the direct estimator of equation (1.4), using the known outcome mechanism, in a single, very large sample of $n = 10,000,000$. As evaluation criteria, we consider the scaled asymptotic bias (i.e., $\sqrt{n}(\psi_{0,\delta} - \psi_{n,\delta,\lambda_n})$), which is expected to decrease with increasing sample size for consistent estimators; the scaled mean squared error (MSE) (i.e., $n\{(\psi_{0,\delta} - \psi_{n,\delta,\lambda_n})^2 + \sigma^2_{n,\lambda_n}\}$), relative to the efficiency bound of the model, which should converge to one for efficient estimators; and the coverage of oracle confidence intervals (with the variance of $\psi_{n,\delta,\lambda_n}$ computed across simulation experiments rather than estimated directly), which should reach the nominal rate irrespective of issues of variance estimation, which are not our focus here. All numerical experiments were performed using version 4.0.3 of the `R` language and environment for statistical computing [133].

Simulation #1: Treatment Mechanism with Constant Variance

The first DGP in our experiments uses the following generating functions for the treatment and outcome mechanism. While the form of the outcome mechanism is a function of the treatment A and baseline covariates $\{W_1, W_2, W_3\}$, we recall that it does not impact the construction of our IPW estimators, only, in two cases (when the criterion of Lemma 1 is used), their selection. In this scenario, the form of the treatment mechanism is chosen as a normal distribution with mean being a function of the baseline covariates $\{W_1, W_2, W_3\}$, and constant variance; thus, accurate estimation of the location parameter is all that is necessary for the conditional density to be well-estimated. Here, the form of the treatment mechanism is $A \mid W \sim$ Normal $\Big(\mu = 2W_1 + W_2 - 2 \cdot (1 - W_1) \cdot W_2, \sigma^2 = 2\Big)$, while that of the outcome mechanism is $Y \mid A, W \sim$ Bernoulli $\Big(p = \text{expit}(3 \cdot (A - 1) + W_1 + 1.5W_2^2 - W_3 - 3 \cdot (1 - W_1) \cdot W_2)\Big)$.

The results of applying our proposed IPW estimators to the estimation of $\psi_{0,\delta}$ are summarized across the 300 simulation experiments in Figure 1.

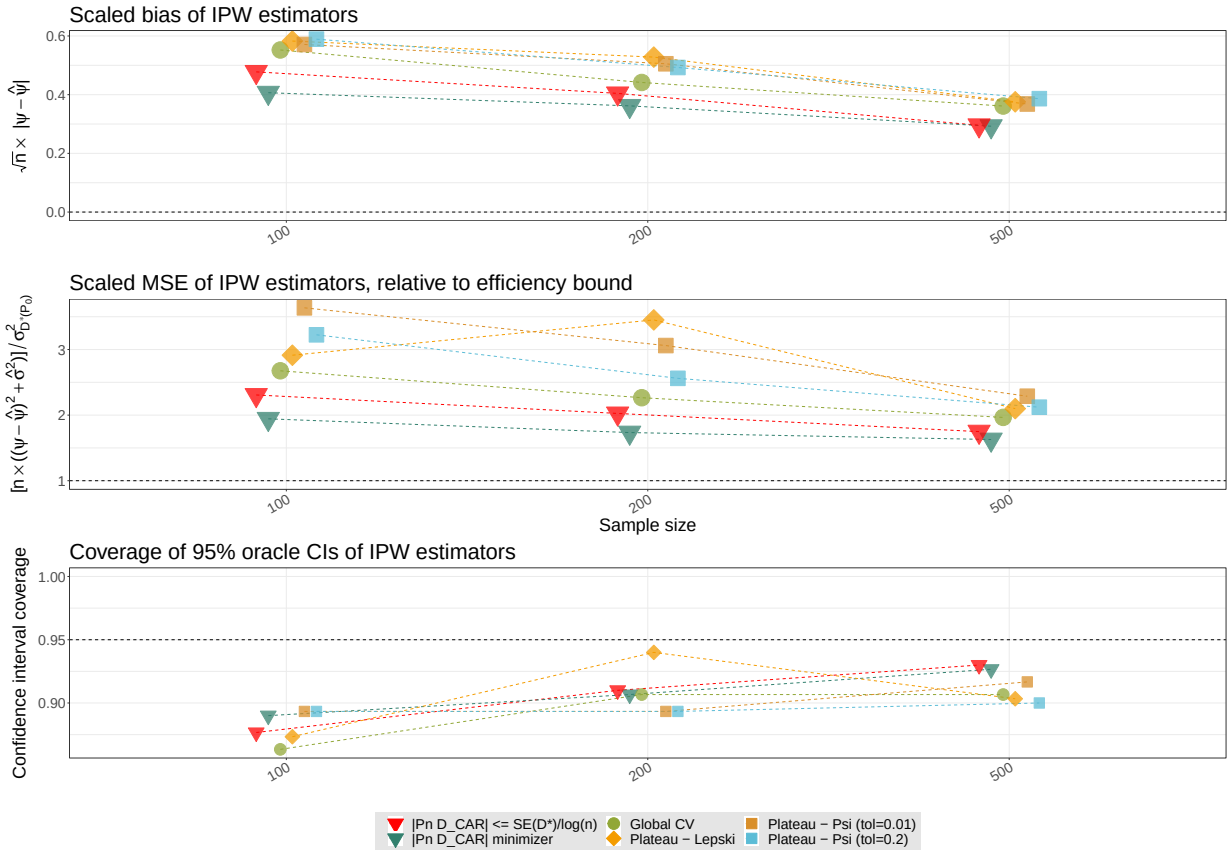

Figure 1: Numerical comparisons of nonparametric IPW estimator variants of $\psi_{0,\delta}$ for $A \sim \text{Normal}(\mu = f(W), \sigma^2 = k)$.

Inspection of Figure 1 reveals generally acceptable performance of all of our IPW estimators, with bias of 0.06 and 0.04 in the worst and best cases, respectively, at $n = 100$; this performance improves to a bias of 0.018 in the worst case and of 0.013 in the best case at $n = 500$. In terms of bias, our IPW estimators using targeted undersmoothing outperform the other variants uniformly across sample sizes, though the difference is not great between the best and worst case biases. Considering the scaled MSE, the IPW estimators using targeted undersmoothing once again dominate the others uniformly across sample sizes. Notably, in terms of this performance measure, the IPW estimator utilizing the cross-validation selector outperforms those using agnostic undersmoothing. This is a surprising finding since cross-validation chooses the optimal estimator of $g_{0,A}$, not necessarily that of $\psi_{0,\delta}$; moreover, this relatively good performance suggests that even cross-validation may make for a reasonably reliable strategy in constructing nonparametric IPW estimators of $\psi_{0,\delta}$. With respect to the empirical coverage of oracle confidence intervals, none of the candidate IPW estimators succeed in attaining the nominal rate, though this is consistent with the prior observation

that none of the estimators are perfectly unbiased at any of the sample sizes. Altogether, the results of this experiment suggest that targeted undersmoothing of the HAL generalized propensity score estimator can be used to construct nonparametric IPW estimators with reasonably good, though not excellent, asymptotic consistency and efficiency.

Simulation #2: Treatment Mechanism with Unequal Mean and Variance Dependent on Baseline

The next scenario is a modification of the previous, in which the form of the treatment mechanism is kept fixed to a normal distribution, though the mean and variance are now modified to both be functions of a subset of the baseline covariates $\{W_1, W_2\}$; W_3 has no impact on the treatment mechanism but does appear in the outcome mechanism, whose forms is a function of the treatment A and all baseline covariates. Perhaps significantly, the form of the treatment mechanism in this scenario demands accurate estimation of both the location and scale parameters of the normal distribution; moreover, the heteroscedasticity with respect to the baseline covariates complicates accurate estimation of the conditional density $g_{0,A}$ relative to the form of the treatment mechanism in the prior scenario. While the form of the outcome mechanism differs from that in the previous scenario, we again do not expect its form to affect the construction of our IPW estimators much. The treatment mechanism takes the form $A \mid W \sim \text{Normal}\left(\mu = W_1 + 2W_2 - 2 \cdot (1 - W_1) \cdot W_2, \sigma^2 = 2W_1 + 0.5(1 - W_1) + W_2\right)$, while the outcome mechanism is $Y \mid A, W \sim \text{Bernoulli}\left(p = \text{expit}(5(A - 2) + W_1 + 3W_2^4 - 2W_3 - 4(1 - W_1)W_2)\right)$.

We summarize the performance of our proposed IPW estimators in terms estimation of $\psi_{0,\delta}$ across the 300 simulation experiments in Figure 2.

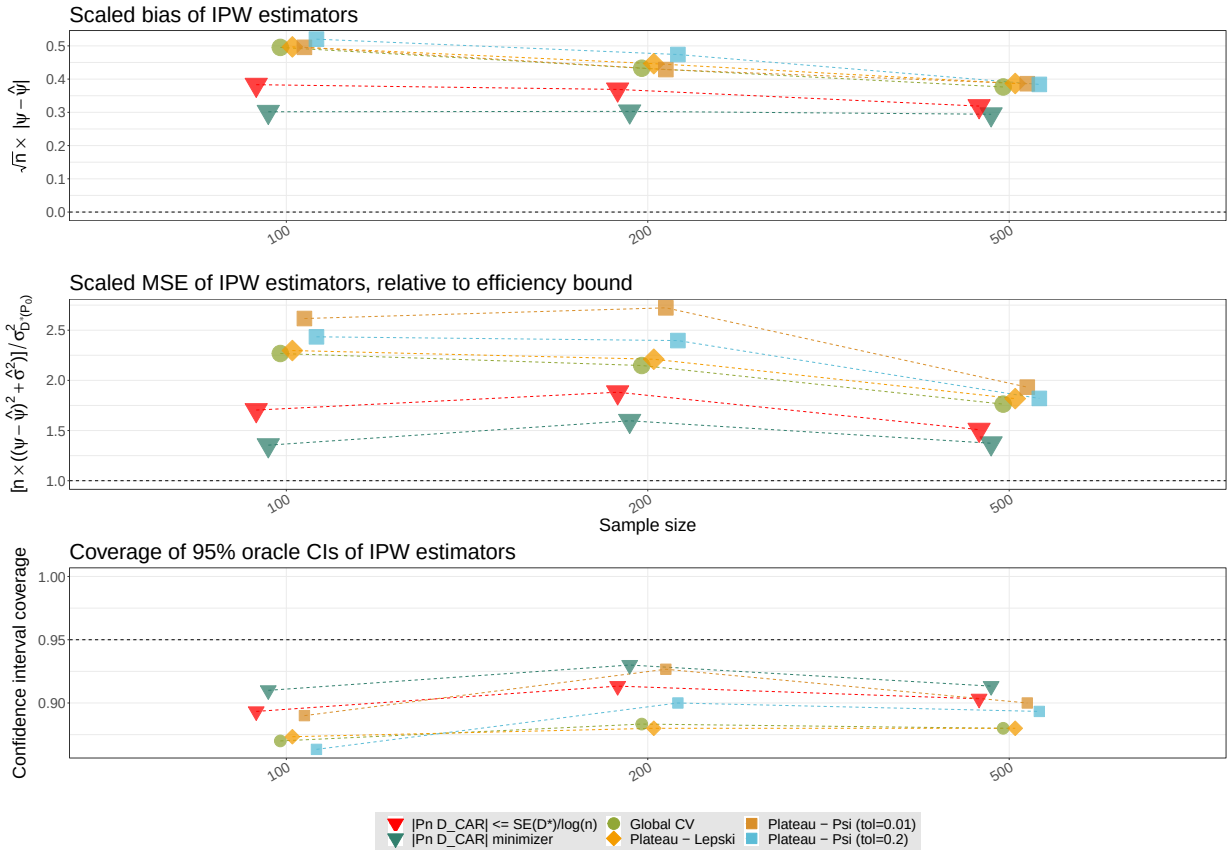

Figure 2: Numerical comparisons of nonparametric IPW estimator variants of $\psi_{0,\delta}$ for $A \sim \text{Normal}(\mu = f_1(W), \sigma^2 = f_2(W))$.

Upon examination, Figure 2 reveals relative performance measures of the IPW estimators very similar to that observed in the prior scenario. In particular, the IPW estimators constructed based on targeted undersmoothing outperform all of the other candidates in terms of both bias and efficiency. In terms of bias, all estimators again achieve acceptable levels of performance: at $n = 100$, bias is 0.052 in the worst case and 0.03 in the best case, while at $n = 500$, the same metrics are 0.018 and 0.013, respectively. Turning now to efficiency, none of the estimators achieve the efficiency bound of the model at the examined sample sizes, though the decreasing trajectory of their scaled MSEs suggests promising performance at larger sample sizes. In this scenario, the IPW estimator based on the cross-validation selector performs similarly to those based on agnostic undersmoothing. As none of our proposed IPW estimators is perfectly unbiased, the constructed oracle confidence intervals fail to attain the nominal coverage rate, consistent with expectations. The results of this experiment echo those of the first — our IPW estimators utilizing targeted undersmoothing outperform the others, though not considerably in any metric.

Simulation #3: Treatment Mechanism with Equal Mean and Variance Dependent on Baseline

We next consider our final experimental scenario, which breaks from the preceding two examples by basing the form of the treatment mechanism on a Poisson distribution, so that the mean and variance are both equally impacted by the relevant baseline covariates. As with the example immediately prior, the treatment mechanism is a function of a subset of the baseline covariates $\{W_1, W_2\}$, with W_3 only impacting the outcome mechanism. As with our prior experiments, the form of the outcome mechanism is not expected to impact our proposed IPW estimators, since estimation of the outcome mechanism only plays a role in our targeted undersmoothing selection procedures. We note that the form of the treatment mechanism results in A taking on discrete values in a fairly large range, unlike the continuous-valued observations that result from the normal distribution appearing in the prior examples; this treatment mechanism's form is possibly more compatible with the generalized propensity score estimator of Algorithm 2, which utilize discretization of A for estimation of the conditional density. For this scenario, the treatment mechanism takes the form $A \mid W \sim \text{Poisson}\left(\lambda = (1 - W_1) + 0.25W_2^3 + 2W_1W_2 + 4\right)$ and outcome mechanism is of the form $Y \mid A, W \sim \text{Bernoulli}\left(p = \text{expit}(A + 2(1 - W_1) + 0.5W_2 + 0.5W_3 + 2W_1W_2 - 7)\right)$.

Numerical evaluation of the performance of our proposed IPW estimators of $\psi_{0,\delta}$ across the 300 simulation experiments is summarized in Figure 3.

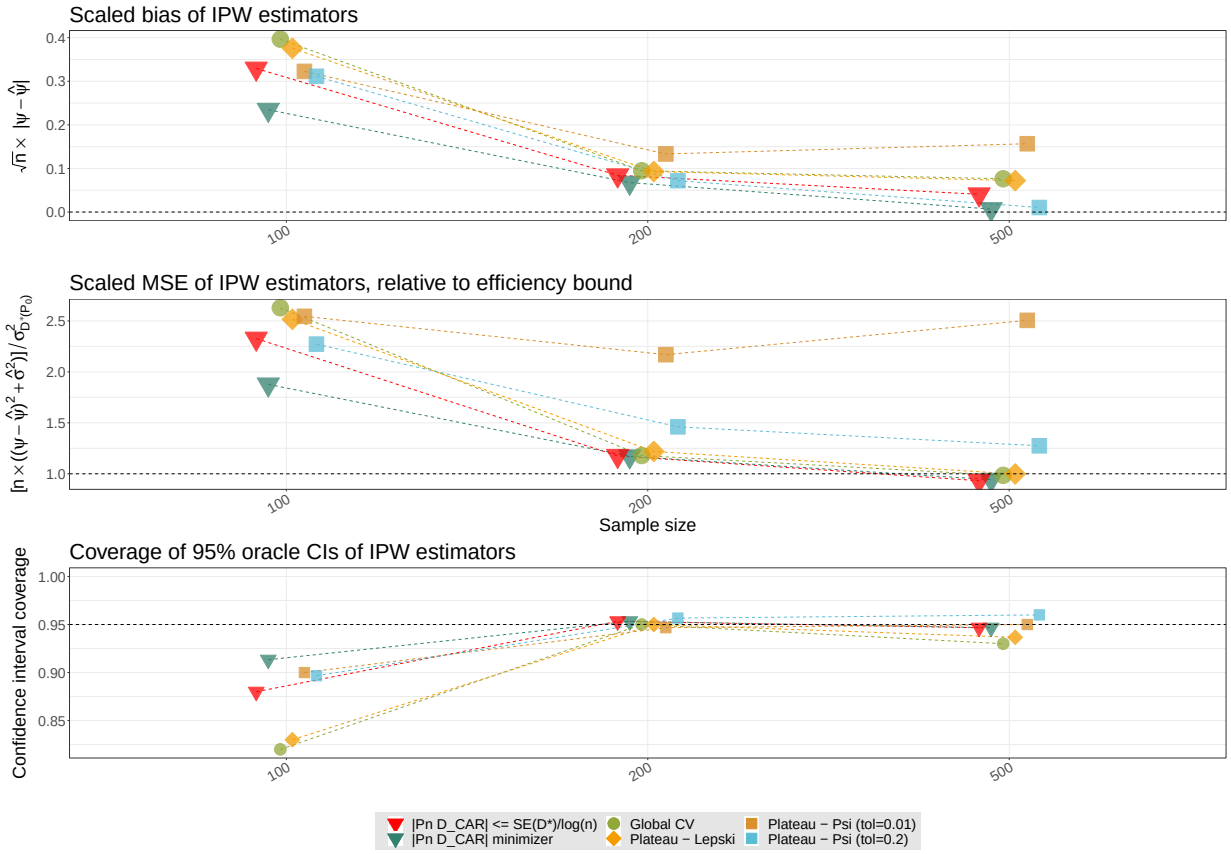

Figure 3: Numerical comparisons of nonparametric IPW estimator variants of $\psi_{0,\delta}$ for $A \sim \text{Poisson}(\lambda = f(W))$.

Figure 3 reveals the best performance of our proposed IPW estimators encountered thus far. In this setting, the IPW estimator variants using targeted undersmoothing outperform the others only at the smallest sample size — that is, at $n = 100$, the IPW estimator based on minimization of the EIF term arising from Lemma 1 achieves the lowest bias and best efficiency. By $n = 500$, most estimator variants are nearly unbiased, with the best performing being IPW estimators minimizing $|P_n D_{\text{DCAR}}|$ via targeted undersmoothing and the less restrictive ($\tau = 0.2$) agnostic undersmoothing selector based on equation (1.12). In terms of efficiency, all candidates but the IPW estimators constructed from agnostic undersmoothing based on equation (1.12) succeed in achieving the efficiency bound, an excellent level of performance. Notably, even the IPW estimator based on the cross-validation selector succeeds in this challenging endeavor, suggesting that it exhibits variance relatively improved beyond that of the other candidates, on account of the fact that it is not similarly unbiased. Unlike the prior scenarios, the oracle confidence intervals of all candidate IPW estimators attain the nominal coverage rate by $n = 200$, with similar performance

at $n = 500$. Importantly, the excellent performance of all of the estimator candidates with respect to this metric suggests that all are capable of providing reliably good performance and that relative performance differences across the candidates may be better ascribed to variance estimation than to point estimation, the latter of which is our principal focus. Though the previously considered scenarios were not discouraging, the results of this set of experiments are quite positive, suggesting that at least a few variants of our proposed IPW estimators may successfully applied to reliably and efficiently estimate $\psi_{0,\delta}$.

1.5 Discussion

The generalized propensity score is a central object in evaluating the causal effects of continuous treatments. While stochastic interventions provide a framework for identifying causal effects of realistic interventions, their formulation too depends on the generalized propensity score. Accordingly, flexible estimators of this key nuisance quantity, relying on recent developments in nonparametric regression, are poised to play important roles in developing consistent and efficient estimators of the causal effects of stochastic interventions. We have provided an initial examination of the role of a flexible regression algorithm, the recently developed highly adaptive lasso estimator, in developing conditional density estimators with favorable theoretical properties. Building on these contributions, we formulated nonparametric IPW estimators of the causal effects of stochastic interventions, previously absent from the causal inference literature. To further improve our IPW estimators, we outlined several selection procedures, to be used in tandem with undersmoothing of our proposed HAL-based conditional density estimators, to allow these novel IPW estimators to achieve the nonparametric efficiency bound, a property previously attainable by doubly robust estimators. In numerical experiments, we examined the relative performance our nonparametric IPW estimators, demonstrating their capability to achieve low bias and attain the efficiency bound in some examples. Several avenues for future investigation remain, including potential improvements to doubly robust estimators that incorporate undersmoothing of the generalized propensity score, which may exhibit higher-order types of efficiency or make doubly robust inference [e.g., 12] possible, and the extension of our nonparametric IPW estimators to more complex settings in which stochastic interventions have proven useful, including causal mediation analysis [e.g., 35].

Chapter 2

Correcting for Biased Sampling

The advent and subsequent widespread availability of preventive vaccines has altered the course of public health over the past century. Despite this success, effective vaccines to prevent many high-burden diseases, including HIV, have been slow to develop. Vaccine development can be aided by the identification of immune response markers that serve as effective surrogates for clinically significant infection or disease endpoints. However, measuring immune response marker activity is often costly, which has motivated the usage of two-phase sampling for immune response evaluation in clinical trials of preventive vaccines. In such trials, the measurement of immunological markers is performed on a subset of trial participants, where enrollment in this second phase is potentially contingent on the observed study outcome and other participant-level information. We propose nonparametric methodology for efficiently estimating a counterfactual parameter that quantifies the impact of a given immune response marker on the subsequent probability of infection. Along the way, we fill in theoretical gaps pertaining to the asymptotic behavior of nonparametric efficient estimators in the context of two-phase sampling, including a multiple robustness property enjoyed by our estimators. Techniques for constructing confidence intervals and hypothesis tests are presented, and an open source software implementation of the methodology, the `txshift` `R` package, is introduced. We illustrate the proposed techniques using data from a recent preventive HIV vaccine efficacy trial.

2.1 Introduction

Ascertaining the population-level causal effects of exposures is a common goal in scientific research. Such effects can be formulated via summaries of the distribution of *counterfactual random variables*, which describe the values a measurement would have taken if a particular level of exposure were assigned to the unit. Often, the exposure of interest is continuous-valued — for example,

the dose of a drug or level of an immune response marker induced by a vaccine. We consider the latter in the context of a phase IIb trial of a vaccine to prevent infection by human immunodeficiency virus (HIV), the HIV Vaccine Trials Network's (HVTN) 505 efficacy trial [67]. A key secondary objective of the trial was to evaluate the role of vaccine-induced immune responses in generating protective efficacy against HIV infection [90]. Identification of immune response markers *causally* related to protection is critical both for understanding of the biological mechanisms of a vaccine and for guiding the development of future vaccines.

To study such relationships, it is natural to consider a dose-response curve that summarizes vaccinated participants' risk of HIV infection as a function of a particular immune response marker. A causal formulation of such a dose-response analysis would consider a (possibly infinite) collection of counterfactual outcomes, each representing the HIV infection risk that would have been observed if all individuals' immune responses had been set to a particular level. Studying how the proportion of infected individuals varies as a function of the level of an immune response marker could provide insights into causal mechanisms underlying the vaccine's effects. Unfortunately, several difficulties arise when considering such a dose-response approach. Nonparametric estimation and inference on the causal dose-response curve is challenging and requires non-standard techniques (e.g., Kennedy et al. [92]). More importantly, this approach may require consideration of counterfactual variables that are scientifically unrealistic. Namely, it may be impossible to imagine a world where every vaccinated participant exhibits high immune responses, simply due to phenotypic variability of participants' immune systems. This calls into question the validity of counterfactual dose-response analysis strategies that evaluate the effects of immune response markers.

An alternative framework for assessing effects of continuous-valued exposures involves counterfactual outcomes resulting from *stochastic* interventions [37, 68]. Whereas static interventions set the same level of an exposure to all units, stochastic interventions instead set exposure level equal to a random draw from a particular distribution. This provides a more flexible approach for defining counterfactual random variables. Indeed, static interventions are a special case of stochastic interventions in which the intervention mechanism is drawn from a degenerate distribution with point mass on a single value. To define meaningful counterfactuals, care must be taken in defining the distribution from which the exposure is drawn. One strategy is to draw from a modified version of the true exposure distribution — the *natural distribution* of exposure under no intervention. For example, one may consider drawing immune response markers from a distribution similar to the naturally observed post-vaccination distribution of immune response markers *but* that has been shifted upwards (or downwards) for some or all participants. Counterfactuals defined by such interventions may be better aligned with plausible future interventions, such as refinements of the current vaccine that provide improved immune responses. Evaluating the population-level risk of

HIV infection under such interventions is useful for several reasons. Firstly, this measure of risk provides a relevant mechanism by which to rank-order immune response markers by their importance for HIV infection risk. Such information could be used in a future phase 2a trial of a refined candidate HIV vaccine to define go/no-go criteria based on immune response marker endpoints for advancing the vaccine to an efficacy trial. Relatedly, the risk measure may be useful for "transport formulas" that predict vaccine efficacy in new settings different from that in the original efficacy trial [121].

The above highlights the need for methodology to identify and estimate population-level causal effects of stochastic interventions; recent work has provided several candidate approaches [37, 68]. These works show conditions for the identification and detail several estimators of parameters of distributions of counterfactuals defined by stochastic interventions. However, these approaches are not directly applicable to studies like HVTN 505 trial, where a two-phase, case-cohort sampling design was used to measure participants' immune responses. Under this design, *all* vaccine recipients diagnosed with HIV-1 infection (i.e., "cases") had their post-vaccination immune responses measured, while only a *random sample* of HIV-uninfected vaccine recipients had immune responses measured [90]. This sampling design complicates the estimation of causal effects, as the cohort definition depends on post-randomization data, namely whether a participant was infected. Rose and van der Laan [143], among others, discuss strategies for efficient estimation under two-phase sampling designs, emphasizing an inverse probability of censoring weighted modification that may be coupled with targeted minimum loss estimation to account for study design. Their approach yields an asymptotically linear estimator so long as the probability of inclusion in the second-phase sample is known by design or estimable via maximum likelihood. This latter requirement precludes usage of their proposed estimators in situations where, for example, sampling probabilities are unknown and may depend on continuous-valued covariates. While the term "two-phase sampling" has traditionally been used to refer to outcome-dependent Bernoulli or without-replacement sampling based on discrete covariates, recent efforts have extended the concept to the usage of continuous-valued covariates in constructing second-phase samples [e.g., 60]. Rose and van der Laan [143] suggested a more complicated procedure that could be appropriate in such settings, but it has neither been evaluated in simulation nor data analysis.

In the present work, we develop estimators of the mean counterfactual outcome under a stochastic intervention when the exposure is measured via two-phase sampling. We provide several contributions to literatures on two-phase sampling and stochastic interventions. To the former, we (i) formalize assumptions needed for efficient nonparametric inference under two-phase sampling; (ii) characterize a multiple robustness of the estimators; and (iii) provide the first comparison of the practical performance of these estimators. Our contributions to the literature on stochastic interventions are (i) a novel estimator of a conditional density that is valid under two-phase sampling,

while achieving a fast convergence rate, a crucial development for generating efficient estimators of the mean counterfactual; and (ii) an extension of nonparametric inference on mean counterfactuals under stochastic interventions using projections onto nonparametric working marginal structural models. Finally, we provide open source `R` packages, `txshift` [72, 73] and `haldensify` [74] that implement of our proposed estimators.

2.2 Preliminaries and Background

Notation, Data, and Target Parameter

Consider data generated by typical cohort sampling represented by the random variable $X = (W, A, Y)$, where $W \in \mathcal{W}$ is a vector of baseline covariates, $A \in \mathcal{A}$ a real-valued exposure, and $Y \in \mathcal{Y}$ an outcome of interest. Initially, we assume access to n independent copies of X, using P_0^X to denote the distribution of X. We assume a nonparametric statistical model $\mathcal{M}^X$ for P_0^X. We denote by $q_{0,Y}$ the conditional density of Y given $\{A, W\}$ with respect to some dominating measure, $q_{0,A}$ the conditional density of A given W with respect to dominating measure μ, and $q_{0,W}$ the density of W with respect to dominating measure ν. We use p_0^X to denote the density of X with respect to the product measure. This density evaluated on a typical observation x may be expressed $p_0^X(x) = q_{0,Y}(y \mid A = a, W = w) q_{0,A}(a \mid W = w) q_{0,W}(w)$.

To define a counterfactual quantity of interest, we introduce a nonparametric structural equation model (NPSEM) [117], which assumes X is generated by the following system of structural equations: $W = f_W(U_W); A = f_A(W, U_A); Y = f_Y(A, W, U_Y)$. Here, f are deterministic functions and $\{U_W, U_A, U_Y\}$ are exogenous random variables such that $U_A \perp U_Y$ and either $U_W \perp U_Y$ or $U_W \perp U_A$, which establishes that conditioning on W is sufficient to control confounding of A and Y.

The NPSEM parameterizes p_0^X in terms of the distribution of the random variables (X, U) and implies a model for the distribution of counterfactual random variables generated by interventions on the data-generating process. For example, a *static intervention* replaces f_A with a real number a. A *stochastic intervention* replaces the value A would naturally assume with a draw from a post-intervention distribution $\tilde{q}_{0,A}(\cdot \mid W)$, where the zero subscript is included to emphasize that $\tilde{q}_{0,A}$ may depend on P_0^X. A static intervention may be viewed as a stochastic intervention where $\tilde{q}_{0,A}(\cdot \mid W)$ places all mass on a single point. Díaz and van der Laan [37] described a stochastic intervention that draws A from a distribution such that for a real number a $\tilde{q}_{0,A}(a \mid W) = q_{0,A}(a - \delta(W) \mid W)$ for a user-supplied shifting function $\delta(W)$. Haneuse and Rotnitzky [68] showed that estimating the effect of this intervention is equivalent with that of an intervention that modifies the value A would naturally assume according to a regime $d(A, W)$. Importantly, the regime $d(A, W)$ may depend

on both the covariates W and the exposure level A that would be assigned in the absence of the regime; consequently, this has been termed a *modified treatment policy* (MTP). Both Haneuse and Rotnitzky [68] and Díaz and van der Laan [38] considered an MTP of the form $d(a, w) = a + \delta(w)$ for $\delta(w) = \gamma \in \mathbb{R}$ if $a + \gamma \leq u(w)$ and $d(a, w) = a$ if $a + \gamma > u(w)$, where $u(w)$ is the maximum value in the support of $q_{0,A}(\cdot \mid W = w)$. This intervention generates a counterfactual random variable $Y_{A+\delta(W)} \coloneqq f_Y(A + \delta(W), W, U_Y)$ whose distribution we denote P_0^δ; we seek to estimate $\psi_{0,\delta} \coloneqq \mathbb{E}_{P_0^\delta}\{Y_{A+\delta(W)}\}$, the mean of this counterfactual outcome.

In the context of HVTN 505, this parameter corresponds to the counterfactual one-year risk of HIV-1 infection had immune response markers of vaccinated participants been increased by γ units relative to the level induced by the current vaccine. This quantity may reflect risk of infection under a next-generation HIV vaccine with improved immunogenicity relative to the vaccine evaluated in HVTN 505. While the magnitude of shifting could generally be allowed to vary with W, we focus on an intervention that uniformly shifts all participants' immune responses by γ, that is, $d(a, w) = a + \gamma$ for all a. Note that for HVTN 505, the parameter of interest is defined only for the vaccine group, making A a post-vaccination marker measuring an HIV-specific immune response. Importantly, it is not conceivable to define the target parameter for placebo recipients since only HIV-negative participants are enrolled in the trial and A is only defined if measured prior to HIV infection; consequently, all relevant placebo recipients have value zero for the marker A, and it is not meaningful to apply $d(a, w)$ to shift the distribution of A.

Analysis of HVTN 505 is complicated by its two-phase design, a technique commonly used for sampling in vaccine efficacy trials. In this sampling scheme, X is not observed all participants. Instead, we observe $O = (W, C, CA, Y) \sim P_0$, where C is an indicator that an observation is included in the second-phase sample; $C_i = 1$ if A is measured on the i^{th} observation and $C_i = 0$ otherwise. By convention, CA denotes that unobserved values of A are set to zero; this arbitrary labeling has no impact on subsequent developments. For each w and y we define $g_{0,C}(y, w) \coloneqq \mathbb{P}(C = 1 \mid Y = y, W = w)$, allowing that the probability of inclusion in the second-phase sample can depend on W and Y. Consequently, the model for P_0 can be expressed as $\mathcal{M} = \{P_{P^X, g_C} : P^X \in \mathcal{M}^X, g_C\}$, that is, P_0 is implied by the pair $\{P_0^X, g_{0,C}\}$. For example, in HVTN 505 all infected participants with samples available for marker measurement at week 28 had immune responses measured, i.e., $g_{0,C}(1, w) = 1$ for all w; however, only a subset of non-infected participants had immune responses measured. We will assume access to an i.i.d. sample $O_1, \ldots, O_n$, denoting its empirical distribution by P_n. We develop efficient nonparametric estimators of $\psi_{0,\delta}$ based on these data.

Identifying the Counterfactual Mean of a Stochastic Intervention

Díaz and van der Laan [37] established that $\psi_{0,\delta}$ is identified by

$$\psi_{0,\delta} = \int_{\mathcal{W}} \int_{\mathcal{A}} \overline{Q}_{0,Y}(a + \delta(w), w) q_{0,A}(a \mid W = w) q_{0,W}(w) d\mu(a) d\nu(w) \ , \tag{2.1}$$

where $\overline{Q}_{0,Y}(a, w) \coloneqq \mathbb{E}_{P_0^X}[Y \mid A = a, W = w]$, the conditional mean of Y given $A = a$ and $W = w$, as implied by P_0^X. Let $Y_{a_i+\delta(w_i)}$ denote the outcome that would have been observed had the observed exposure been, possibly counter-to-fact, set to $a_i + \delta(w_i)$; identification of the causal estimand of interest by equation (2.1) is established under several assumptions: consistency ($Y_{a+\delta(w)} = Y$ in the event $A = a + \delta(w)$); no interference ($Y_{i,a_i+\delta(w_i)}$ does not depend on $a_j + \delta(w_j)$ for $i \neq j$); no unmeasured confounding ($A \perp\!\!\!\perp Y_{a+\delta(w)} \mid W = w$); and positivity ($a \in \mathcal{A} \implies a + \delta(w) \in \mathcal{A} \mid W = w$ for all $w \in \mathcal{W}$). Importantly, even when these untestable assumptions go unsatisfied, the statistical parameter appearing in equation (2.1) has a straightforward interpretation: it is the adjusted mean of the outcome Y under the contrast $A + \delta(W)$, marginalizing over strata of potential baseline confounders W [37, 179].

The positivity assumption required to establish equation (2.1) is unlike that required for static or dynamic interventions. In particular, it does not require that the post-intervention exposure density place mass across all strata defined by W. Instead, for $\overline{Q}_{0,Y}$ to be well-defined, we require that the density of the exposure mechanism be bounded when the post-intervention exposure mechanism is nonzero, i.e., $0 < q_{0,A}(A \mid W)$ when $q_{0,A}(A - \delta(W) \mid W) \neq 0$, which is satisfied by our choice of $\delta(W)$.

Díaz and van der Laan [37] further provided the efficient influence function (EIF) of $\psi_{0,\delta}$ with respect to a nonparametric model. The EIF evaluated on a typical full-data observation x can be written

$$D^F(P_0^X)(x) = H(a, w)\{y - \overline{Q}_{0,Y}(a, w)\} + \overline{Q}_{0,Y}(a + \delta(w), w) - \psi_{0,\delta}, \tag{2.2}$$

where $H(a, w) = \mathbb{1}(a < u(w)) q_{0,A}(a - \delta(w) \mid w) / q_{0,A}(a \mid w) + \mathbb{1}(a + \delta(w) \geq u(w))$.

Correcting for Two-Phase Sampling

The subject of two-phase sampling has long been discussed in the statistical literature [112, 105, 192]. Recent estimation strategies include, among others, methods based on parametric models of the sampling mechanism [18], weighted semiparametric estimators [141], nonparametric maximum likelihood [19], and re-calibration [51].

Rose and van der Laan [143] study of nonparametric efficiency theory in two-phase sampling designs and provide a representation of the EIF of a target parameter of the full data distribution

when the observed data are generated via two-phase sampling. Based on these results, the EIF in the present problem is

$$D(G_0, g_{0,C}, D^F(P_0^X))(o) = \frac{c}{g_{0,C}(y,w)} D^F(P_0^X)(o) - \left(\frac{c}{g_{0,C}(y,w)} - 1\right) G_0(y,w)\,, \tag{2.3}$$

where $D^F(P_0^X)$ is the EIF in equation (2.2), and $G_0(y,w) := \mathbb{E}_{P_0}[D^F(P_0^X)(O) \mid C = 1, Y = y, W = w]$.

Rose and van der Laan [143] proposed two estimation strategies. The first — which we call the reweighted estimator — incorporates inverse probability weights based on known or estimated values of the second-phase sampling probability $g_{0,C}$ to a targeted minimum loss (TML) estimator. The estimator is shown to be asymptotically linear and efficient when $g_{0,C}$ is known or can be estimated using maximum likelihood. On the other hand, their second estimator can be applied in settings where the sampling design is unknown and must be estimated using nonparametric regression. However, the authors did not provide a formal study of the theoretical properties of this estimator nor numerical evaluations. Owing to its complexity, examples of this approach are limited [e.g., 20]. We aim to fill in these gaps by providing formal theory establishing conditions under which this estimator achieves asymptotic efficiency as well as numerical studies demonstrating its performance in the stochastic intervention context.

2.3 Methodology

We utilize two frameworks for estimation: the one-step framework [127] and TML estimation [180]. Both develop in two stages. In the first stage, we construct initial estimators of key nuisance quantities, while in the second stage we perform a bias-correction based on the estimated EIF. The one-step bias correction updates an initial substitution estimator by adding the empirical mean of the estimated EIF, while the TML estimation framework uses a univariate logistic tilting model to build a targeted estimator of $\overline{Q}_{0,Y}$ that is subsequently used to construct a plug-in estimator.

Estimating Nuisance Parameters

Our general strategy for estimating nuisance parameters relies on first using the entire observed data set to estimate the second-phase sampling probabilities, $g_{0,C}$. Subsequently, inverse probability of sampling weights based on these estimates are used to generate estimates of relevant full data quantities using data available only on observations in the second-phase sample. These quantities include the outcome regression $\overline{Q}_{0,Y}$, the exposure density $q_{0,A}$, and the joint distribution of covariates and exposure, which we denote by $Q_{0,AW}$. Finally, estimates of full data quantities are used

to estimate G_0, the conditional mean of the full data EIF given Y and W amongst observations included in the second-phase sample.

Excepting $Q_{0,AW}$, which we estimate using an inverse probability of sampling weighted empirical distribution, we describe both parametric and flexible, data adaptive estimators. The data adaptive estimators are more parsimonious with our theoretical developments, which pertain to nonparametric-efficient estimation; nevertheless, our developments hold equally well for parametric working models. In Theorem 1, we detail assumptions on the stochastic behavior of estimators of these nuisance functions and relate these to the behavior of the resultant estimator of the target parameter.

An estimator of the sampling mechanism $g_{0,C}$ could be derived from any classification method (e.g., logistic regression), in which $\mathbb{P}_{P_0}(C = 1 \mid Y, W)$ is estimated using the full sample; however, nonparametric or semiparametric estimation may be preferable depending on the availability of information about the two-phase sampling design.

To generate an estimate $Q_{n,AW}$ of the full data joint distribution of (A, W), we use a stabilized inverse probability weighted empirical distribution. For a given (a, w), $Q_{n,AW}(a, w) := \sum_{i=1}^{n} C_i / g_{n,C}(Y_i, W_i) \mathbb{1}(A_i \leq a, W_i \leq w) / \sum_{i=1}^{n} C_i / g_{n,C}(Y_i, W_i)$. To estimate $\overline{Q}_{0,Y}$, one may again use any classification or regression model, where Y is the outcome and functions of A and W are included as predictors. In fitting this model, inverse probability of sampling weights $C_i / g_{n,C}(Y_i, W_i)$ for $i = 1, \ldots, n$, are included to account for the two-phase sampling design. Any valid regression estimator may be leveraged for this purpose, so long as the implementation of the estimator respects the inclusion of sample-level weights; in practice, we recommend the use of a semiparametric or nonparametric estimator. We denote by $\overline{Q}_{n,Y}(a, w)$ the estimate evaluated on a data unit with $A = a, W = w$.

The simplest strategy for estimating the generalized propensity score $q_{0,A}$ is to assume a parametric working model and use parametric regression to generate suitable density estimates. Unfortunately, most such approaches do not allow for flexible modeling of $q_{0,A}$. The relative dearth of available estimators of a conditional density motivated our development of a novel estimator that accounts for two-phase sampling designs. We detail this approach in Algorithm 2 of Chapter 1 and provide an implementation of this proposal in the `haldensify` `R` package [74], described in Section 5.4 of Chapter 5. Going forward, we denote by $q_{n,A}(a \mid w)$ the estimated conditional density of A given $W = w$, evaluated at $a \in \mathcal{A}$.

The final nuisance parameter that must be estimated is G_0, the conditional mean of the random variable $D^F(P_0^X)(O)$ given (Y, W) amongst those included in the second-phase sample. To estimate this quantity, we generate a pseudo-outcome as follows. First, define the substitution estimator $\psi_{n,\delta} := \int \overline{Q}_{n,Y}(a + \delta(w), w) dQ_{n,AW}(a, w)$, and the auxiliary term $H_n(a, w) := \mathbb{1}(a < u(w)) q_{n,A}(a - \delta(w) \mid w) / q_{n,A}(a \mid w) + \mathbb{1}(a + \delta(w) \geq u(w))$. Using these quantities, for all i such

that $C_i = 1$, we compute $D^F_{n,i} := H_n(A_i, W_i)\{Y_i - \overline{Q}_{n,Y}(A_i, W_i)\} + \overline{Q}_{n,Y}(A_i + \delta(W_i), W_i) - \psi_{n,\delta}$. A simple estimation strategy for G_0 is to adopt a parametric working model and fit, for example, a linear regression of the pseudo-outcome $D^F_{n,i}$ on basis functions of Y and W. Importantly, since G_0 is defined as a conditional expectation with respect to the observed data distribution, we need not include inverse probability of sampling weights in this regression estimate. While a parametric working model for G_0 is permissible, given the complexity of the object, correct specification of this model is likely challenging and we recommend more flexible approaches. We let $G_n(Y_i, W_i)$ denote the value of the chosen regression estimator evaluated on the i^{th} observation $i = 1, \ldots, n$.

Efficient Estimation

One-Step Estimator

Based on the estimated nuisance functions detailed above, efficient estimators may be constructed using either of the one-step or targeted minimum loss estimation frameworks. The one-step estimator adds the empirical mean of the estimated EIF to the initial plug-in estimator, $\psi^+_{n,\delta} := \psi_{n,\delta} + n^{-1} \sum_{i=1}^n \left[C_i / g_{n,C}(Y_i, W_i) D^F_{n,i} - \left\{ C_i / g_{n,C}(Y_i, W_i) - 1 \right\} G_n(Y_i, W_i) \right]$. The resultant augmented one-step estimator $\psi^+_{n,\delta}$ relies on the nuisance functions estimators $(\overline{Q}_{n,Y}, g_{n,A}, G_n, g_{n,C})$. Theorem 1 details sufficient assumptions on these estimators for ensuring that the one-step is asymptotically efficient.

Targeted Minimum Loss Estimator

An asymptotically linear TML estimator of $\psi_{0,\delta}$ may be constructed by using inverse probability of sampling weights to update the initial estimator $\overline{Q}_{n,Y}$ to an estimator $\overline{Q}^\star_{n,Y}$. An updated plug-in estimator is then constructed, $\psi^\star_{n,\delta} := \int \overline{Q}^\star_{n,Y}(a + \delta(w), w) dQ_{n,AW}(a, w)$. This updated estimator $\overline{Q}^\star_{n,Y}$ is constructed in a single iteration as follows.

1. Define a working logistic regression model for the conditional mean of C given $\{Y, W\}$, using the logit of the initial estimate of the censoring mechanism, $\text{logit}(g_{n,C})$, as an offset and with covariate $(G_n / g_{n,C})$. The parameter $\xi \in \mathbb{R}$ corresponding to the covariate may be estimated by maximum likelihood, producing an estimate ξ_n. Following estimation of ξ_n, this working model yields $g^\star_{n,C}$, an updated estimate of the censoring mechanism.

2. Next, define a working logistic regression model for the conditional mean of Y given $\{A, W\}$, taking the initial estimate of the outcome mechanism $\text{logit}(\overline{Q}_{n,Y})$ as an offset and with covariate H_n. The parameter $\epsilon \in \mathbb{R}$ can be estimated via weighted logistic regression (with

weights $C_i/g^{\star}_{n,C}(Y_i, W_i)$) to yield an estimate ϵ_n of ϵ. Using ϵ_n and this working model, we may update the outcome mechanism to $\overline{Q}^{\star}_{n,Y}$.

The targeting steps are carried out based on local least favorable parametric submodels, generally requiring only a single iteration for convergence. When the first step of this procedure is omitted, the resultant TML estimator is equivalent to the reweighted estimator of Rose and van der Laan [143]. The additional step allows our estimator to attain asymptotic linearity in a broader set of circumstances. That is, while the reweighted estimator requires that the sampling weights be known or be estimable at a parametric rate, our approach allows for the use of more flexible estimators of sampling weights. Algorithm 3, presented in Section 2.7, formalizes the proposed procedure.

Asymptotic Analysis of Efficient Estimators

We establish the asymptotic efficiency of our estimators in Theorem 1. The theorem depends on a several regularity conditions, which are discussed in Section 2.7. The theorem is provided in the context of the TML estimator, but, with a similar set of assumptions, the same result holds for the one-step estimator; for brevity, we omit this analogous result. In the sequel, $D^F(\overline{Q}_{0,Y}, q_{0,A})$ and $D^F(P_0^X)$ are used interchangeably since D^F depends on P_0^X only through $\overline{Q}_{0,Y}$ and $q_{0,A}$.

Theorem 1 (Asymptotic linearity and efficiency of the TML estimator $\psi^{\star}_{n,\delta}$)**.** *Under conditions 1-6,* $n^{1/2}\left(\psi^{\star}_{n,\delta} - \psi_{0,\delta}\right) = n^{-1/2}\sum_{i=1}^{n} D(G_0, g_{0,C}, D^F(\overline{Q}_{0,Y}, g_{0,A}))(O_i) + o_p(1)$.

An immediate corollary of Theorem 1 is that $\psi^{\star}_{n,\delta}$ is asymptotically efficient, since it is an asymptotically linear estimator with influence function equal to the efficient influence function. Moreover, the central limit theorem implies that the scaled, centered estimator converges in distribution to a mean-zero Gaussian random variable with variance matching that of the EIF (i.e., $\mathbb{E}_{P_0}\{D^2(G_0, g_{0,C}, D^F(\overline{Q}_{0,Y}, g_{0,A}))(O)\}$).

The proof of Theorem 1 is given in Section 2.7. The conditions of the theorem are standard in semiparametric inference problems, essentially requiring a sub-parametric rate of convergence of each of the nuisance estimators to their true counterparts in terms of an $L^2(P_0)$ norm, a Donsker class condition on the EIF evaluated at the estimated nuisance parameters, and $L^2(P_0)$-consistency of this same object.

In particular, condition 1 requires that the EIF equation be solved and is satisfied by our proposed estimators, while condition 6 requires that the estimated EIF fall in a Donsker class. This latter requirement may be satisfied by using highly adaptive lasso (HAL) regression for all nuisance parameters or avoided entirely by a particular variant of cross-validation [94, 199, 25]. Such

an estimator enjoys the same asymptotic properties as our non-sample-splitting estimator while eschewing the Donsker class condition.

Conditions 3–5 address the behavior of nuisance parameter estimators. Specifically, condition 3 requires that $g_{n,C}$ and G_n converge in $L^2(P_0)$ norm to their true counterparts while condition 4 necessitates neglibility of a second-order remainder term arising from convergence of $q_{n,A}$ and $\overline{Q}^{\star}_{n,Y}$ to their true counterparts. In the same vein, condition 5 is satisfied by the EIF evaluated at nuisance parameter estimates converging to the EIF evaluated at the true nuisance functions. With respect to these conditions, we note that the HAL regression estimator has been shown to achieve a sufficiently fast rate of convergence so as to satisfy these convergence requirements [167, 13] under the assumption that the true regression function is right-hand continuous with left-hand limits and bounded sectional variation norm. This provided further motivation for our development of a HAL-based conditional density estimator. To increase the applicability of our theorem, our simulation studies and analysis of the HVTN 505 data utilize HAL.

Condition 2 requires that the true sampling mechanism $g_{0,C}$ be bounded away from zero by a (small) positive constant. It is required to ensure that the two-phase sampling procedure does not systematically censor particular strata; the same bound holding for the estimate $g^{\star}_{n,C}$ is required for consistency of the estimator in $L^2(P_0)$ norm. While many of the conditions of the theorem stipulate that the nuisance parameters converge to their true counterparts in large samples, in finite samples, it may be beneficial to avoid small values of the sampling probability $g_{n,C}$. This can be achieved in an ad-hoc way by truncation or more formally via collaborative targeted minimum loss estimation [173].

Multiple Robustness of Efficient Estimators

The EIF of our estimators enjoys a *multiple robustness* property, which allows our estimators to achieve consistency even in situations where certain combinations of nuisance parameters are inconsistently estimated.

Lemma 2 (Multiple robustness of the EIF)**.** *Let* $(G, g_C, \overline{Q}_Y, q_A)$ *denote the limits of the nuisance estimators* $(G_n, g^{\star}_{n,C}, \overline{Q}^{\star}_{n,Y}, q_{n,A})$ *in probability. Suppose either of the following two conditions hold (i)* $G = G_0$ *and either* $\overline{Q}_Y = \overline{Q}_{0,Y}$ *or* $q_A = q_{0,A}$*; (ii)* $g_C = g_{0,C}$ *and either* $\overline{Q}_Y = \overline{Q}_{0,Y}$ *or* $q_A = q_{0,A}$*. Then* $\psi^{\star}_{n,\delta} \xrightarrow[p]{} \psi_{0,\delta}$.

In the case of the one-step estimator, the initial nuisance function estimates $g_{n,C}$ and $\overline{Q}_{n,Y}$ are used instead. The lemma implies that our efficient estimators will be asymptotically consistent if at least one of $(G_0, g_{0,C})$ and one of $(\overline{Q}_{0,Y}, q_{0,A})$ are consistently estimated.

Confidence Intervals and Hypothesis Tests

Theorem 1 established the limiting distribution of our efficient estimators. From the limit distribution, inference for either estimator may be attained in the form of Wald-type confidence intervals and corresponding hypothesis tests.

Consider the null and alternative hypotheses $H_0 : \psi_{0,\delta} = 0$ and $H_1 : \psi_{0,\delta} \neq 0$, and denote by $\psi_{n,\delta}$ either the TML estimator $\psi^{\star}_{n,\delta}$ or the one-step estimator $\psi^{+}_{n,\delta}$. An asymptotic $(1-\alpha)$ Wald-type confidence intervals is $\psi_{n,\delta} \pm z_{\left(1-\alpha/2\right)}\sigma_n/n^{1/2}$, while a p-value for a hypothesis test that $\psi_{0,\delta} = 0$ can be computed as $2\left\{1 - \Phi\left(n^{1/2} \mid \psi_{n,\delta} \mid /\sigma_n\right)\right\}$, where σ_n^2 is the empirical variance of the estimated EIF, $\Phi(\cdot)$ is the CDF of the standard normal distribution, and $z_{\left(1-\alpha/2\right)}$ is the $1-\alpha/2$ standard normal quantile.

These procedures are asymptotically justified under the conditions of Theorem 1. Importantly, while multiple robustness implies that consistent estimation of $\psi_{0,d}$ is possible under inconsistent estimation of some nuisance parameters, the validity of confidence intervals and hypothesis tests requires consistent estimation of *all* nuisance parameters.

2.4 Simulation Studies

The proposed estimators were evaluated using two simulation experiments. In the first, we compare our proposed estimators to alternative estimators proposed in the literature. To highlight the benefits offered by our approach over the simple reweighted estimator of Rose and van der Laan [143], we focus on how estimation of $g_{0,C}$ influences the estimator performance comparing standard logistic regression to the highly adaptive lasso in the construction of $g_{n,C}$. In a second, we evaluate our estimators in a data-generating mechanism inspired by HVTN 505. We compare the relative performance of proposed one-step and TML estimators. These results are detailed in Section 2.7.

We generated data by drawing covariates $W_1 \sim \text{Normal}(3,1)$, $W_2 \sim \text{Bern}(0.6)$, and $W_3 \sim \text{Bern}(0.3)$, exposure $A \mid W \sim \text{Normal}(2(W_2+W_3),1)$, outcome $Y \mid A,W \sim \text{Bern}(\text{expit}((W_1+W_2+W_3)/3-A))$ and sampling probability, $C \mid Y,W \sim \text{Bern}(\text{expit}((W_1+W_2+W_3)/3-Y))$. We sampled n i.i.d. observations, for $n \in \{100,400,900,1600,2500\}$, from this data-generating process and used the resultant data to estimate the target parameter with each of the estimators considered. This was repeated 1000 times. We considered estimation of $\psi_{0,\delta}$ for $\delta \in \{-0.5,0,0.5\}$, where the corresponding true values $\psi_{0,\delta}$ were $\{0.501,0.415,0.333\}$.

We compared the reweighted estimators of Rose and van der Laan [143] to our proposed estimators. For reference, we also present the results of a naive estimate that ignores the two-phase

sampling design. In each of these three cases, we consider one-step and TML estimators, giving six estimators in total. Each estimator was constructed by estimating the exposure mechanism $q_{n,A}$ and outcome mechanism $\overline{Q}_{n,Y}$ via maximum likelihood based on correctly specified parametric models, while $g_{n,C}$ was constructed using either logistic regression or the highly adaptive lasso. Based on theory, we hypothesized that when $g_{n,C}$ is estimated using logistic regression, both the reweighted estimator and our proposed estimator should be asymptotically linear, which would be supported by observing that the bias of the estimators is $o_p(n^{-1/2})$. On the other hand, when $g_{n,C}$ using the highly adaptive lasso), the reweighted estimators should not achieve asymptotic linearity, while our proposed estimators should. The naive estimators, which make no adjustment for the two-phase sampling design, were expected to perform poorly throughout.

We compared all estimators in terms of their bias (scaled by $n^{1/2}$), mean squared-error (scaled by n), and coverage of 95% Wald-style confidence intervals. Figure 4 summarizes our findings for the case $\delta = 0.5$; results for $\delta = 0$ and $\delta = -0.5$ are presented in Section 2.7.

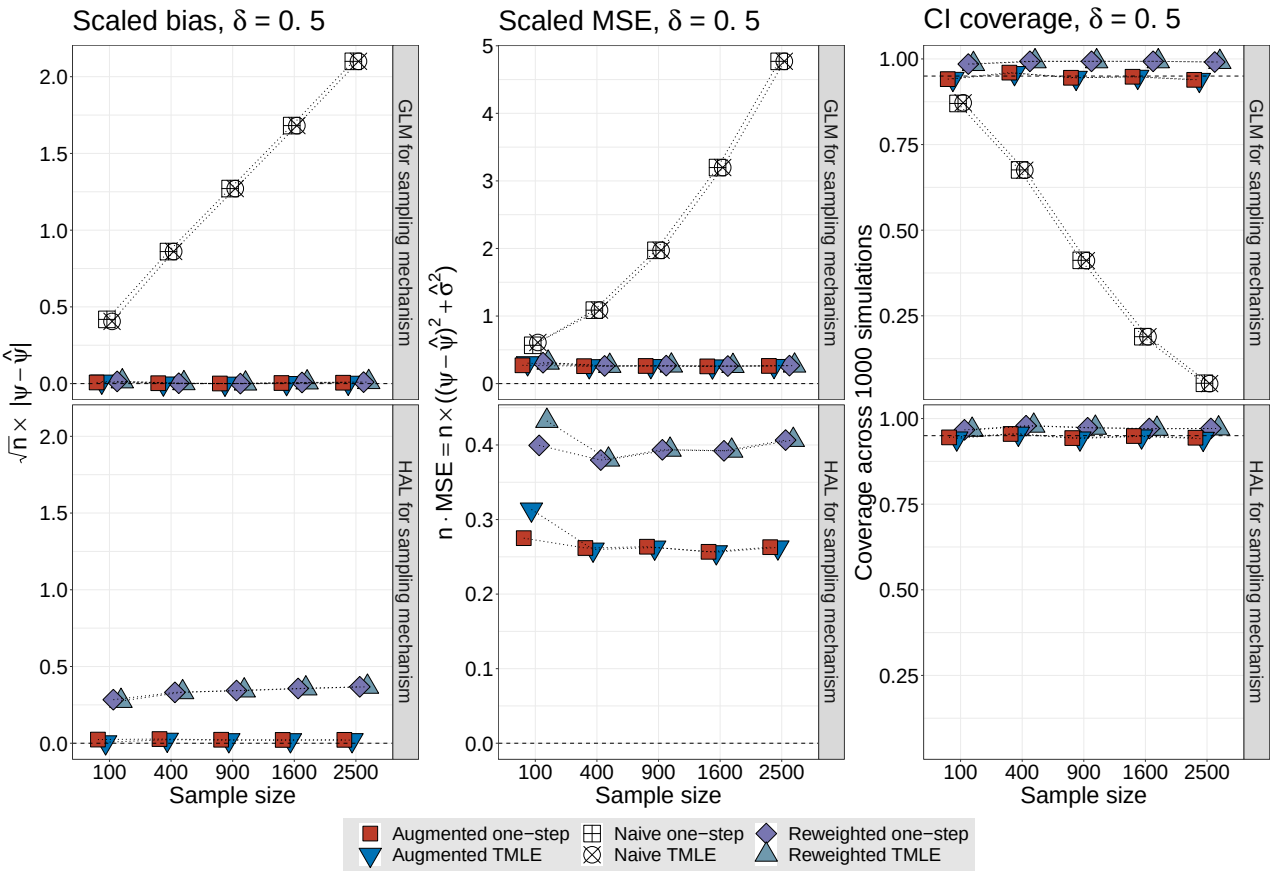

Figure 4: Comparison of six estimation strategies for $\psi_{0,\delta}$ for $\delta = 0.5$, across 1000 Monte Carlo simulations for each of five sample sizes. The naive estimators do not make use of the estimated sampling mechanism $g_{n,C}$, so their performance is displayed only in the upper panel, in the interest of visual economy.

When the sampling mechanism is estimated via a correctly specified parametric model (upper panel), the reweighted and our proposed estimators behave as expected, with low bias and stable MSE. However, the reweighted estimators display coverage exceeding 95%, while our proposed estimators achieve nominal coverage. This occurs because the influence function that is basis for the standard error estimates does not include a first-order contribution resulting from estimation of the sampling mechanism resulting in a conservative standard error estimate. Unsurprisingly, the naive estimator performed poorly in all sample sizes, highlighting the importance of accounting for sampling design.

When the sampling mechanism was estimated using HAL (lower panel), the reweighted estimators do not attain asymptotic linearity, as evidenced by the scaled bias and MSE increasing with sample size. On the other hand our proposed estimators have small bias and MSE approaching the

efficiency bound, thus demonstrating the benefits of the additional effort required to produce our estimators over the simpler reweighted estimators.

Our second simulation study (see Section 2.7) showed that the efficient estimators provide reliable performance in a setting similar to HVTN 505. Importantly, this setting incorporates both continuous and binary baseline covariates and a rare outcome (≈5% incidence). We examine the performance of our proposed one-step and TML estimators at a sample size of $n = 1400$ across $\delta \in \{-2, -1.5, -1, 0.5, 0, 0.5, 1, 2\}$ and all nuisance parameters were estimated via HAL. We found that the proposed estimators achieve low bias and MSE, as well as empirical coverage of confidence intervals near the nominal rate. Overall, the TML estimator had slightly better performance than the one-step estimator.

2.5 Application to the HVTN 505 Trial

HVTN 505 enrolled 2504 HIV-negative participants and randomized participants 1-to-1 to receive an active vaccine or placebo. The one-year incidence of HIV-1 infection was about 1.8% per person-year in the vaccine arm and 1.4% per person-year in the placebo arm, during primary follow-up for HIV-1 acquisition (between week 28 and month 24; the same period as was used for assessment of immune correlates). Blood was drawn at the week 26 visit and immune responses measured for all HIV-1 cases diagnosed between week 28 and month 24 and a stratified random sample of uninfected controls [90]. The two-phase sampling of vaccine-recipient controls sampled five controls per case without-replacement within each of eight baseline covariate strata defined by categories of body mass index and race/ethnicity (White, Hispanic, Black). Janes et al. [90] and Fong et al. [52] analyzed these immune responses, and both found CD4+ and CD8+ polyfunctionality scores to be associated with risk of HIV-1 infection status by month 24.

We examined how a range of posited shifts in standardized polyfunctionality scores of the CD4+ and CD8+ immune markers (A) would impact the mean counterfactual risk of HIV-1 infection (Y) in vaccine recipients. We considered *standardized* polyfunctionality scores, so that our pre-specified grid of shifts $\delta \in \{-2.0, -1.5, -1.0, -0.5, 0.0, 0.5, 1.0, 1.5, 2.0\}$ can be interpreted as shifts on the standard deviation (sd) scale. We present results based on our TML estimator; results for the one-step estimator were similar. To summarize the relationship between the mean counterfactual risk of HIV-1 infection and shifts in polyfunctionality scores, a working marginal structural model (MSM) was constructed, as detailed in Section 2.7. Our augmented TML estimator $\psi^{\star}_{n,\delta}$ requires the construction of initial estimators of all nuisance functions.

The conditional probability of inclusion in the second-phase sample was estimated using HAL, adjusting for age, sex, race/ethnicity, body mass index, and a behavioral risk score for HIV-1

infection. The density $q_{n,A}$ of the CD4+ or CD8+ polyfunctionality scores (A), conditional on the same set of covariates (W), was estimated using our proposed HAL-based conditional density estimator. The outcome regression $\overline{Q}_{0,Y}$, which estimated the risk of HIV-1 infection by 24 months (Y) given polyfunctionality score and baseline covariates, was estimated using super learner [176] (as detailed in Section 2.7). The pseudo-outcome regression, G_n, was fit via HAL.

Results of applying our estimation procedure separately to both the CD4+ and CD8+ polyfunctionality scores are presented in Figures 5 and 6.

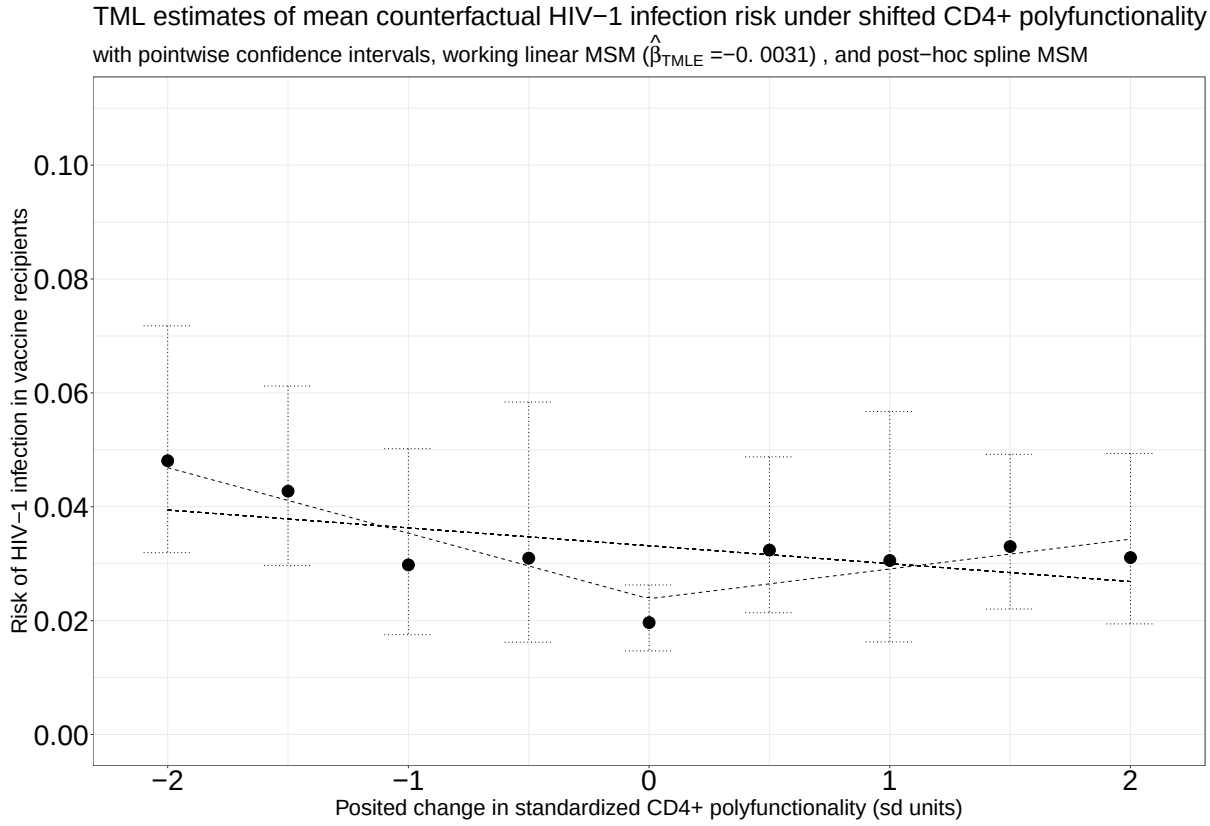

Figure 5: TML estimates of counterfactual HIV-1 infection risk in vaccinees under stochastic interventions on the CD4+ standardized polyfunctionality score. A linear working MSM (postulated *a priori*), with estimated slope $\hat{\beta}_{\text{TMLE}}$, summarizes the effect of shifting the polyfunctionality score on the HIV-1 infection risk, while a V-shaped spline model (constructed post-hoc) traces the profile of counterfactual HIV-1 risk changes in δ.

Examination of the point estimates and confidence intervals of $\psi_{0,\delta}$ in Figure 5 reveals that downshifts in the CD4+ polyfunctionality score led to a small increase in estimated HIV-1 infection risk among vaccine recipients. For example, examining the individual point estimates, a shift of two standard units lower in the CD4+ polyfunctionality score was found to at least double the

counterfactual risk of HIV-1 infection. The estimated slope parameter of the working MSM $\hat{\beta}_{\text{TMLE}}$ pointed to an estimated decrease in risk of about -0.3% per standard unit of CD4+ polyfunctionality change.

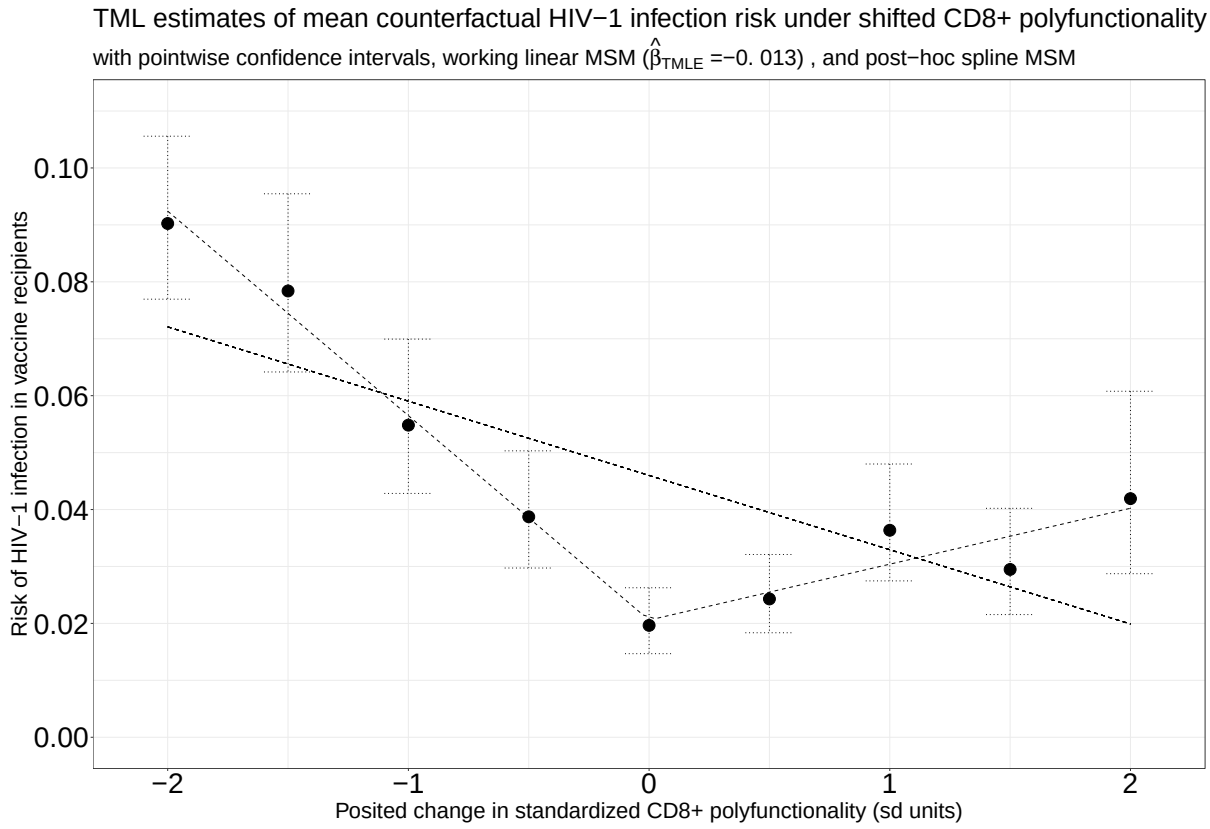

Figure 6: TML estimates of counterfactual HIV-1 infection risk in vaccinees under stochastic interventions on the CD8+ standardized polyfunctionality score. An linear working MSM (postulated *a priori*), with estimated slope $\hat{\beta}_{\text{TMLE}}$, summarizes the effect of shifting the polyfunctionality score on the HIV-1 infection risk, while a V-shaped spline model (constructed post-hoc) traces the profile of counterfactual HIV-1 risk changes in δ.

The estimated result of shifts in the polyfunctionality score of the CD8+ immunological marker displayed a markedly stronger relationship with the risk of HIV-1 infection, as detailed in Figure 6. Positive shifts of the standardized CD8+ polyfunctionality score beyond those observed in the trial do not appear to have a strong effect on HIV-1 infection risk; confidence intervals for counterfactual risk estimates for all $\delta \geq 0$ overlap. On the other hand, shifts that lower the CD8+ polyfunctionality score display a negative linear trend; moreover, confidence intervals for HIV-1 risk estimates at all $\delta < 0$ do not overlap with those of the estimate at $\delta = 0$. While this may be taken to indicate that decreases in CD8+ marker activity adversely affect the risk of HIV-1 infection, we note that this

evidence should be weighed against the fact that all point estimates for $\delta \neq 0$ are, in fact, higher than that at $\delta = 0$; thus, an abundance of caution is warranted in drawing conclusions as to whether shifted CD8+ polyfunctionality score would have improved the HVTN 505 vaccine. Still, it may be informative that the counterfactual HIV-1 infection risk is over four times that observed in the HVTN 505 trial at the largest negative shift considered.

Overall, the results of our analyses support the conclusions of Janes et al. [90] and Fong et al. [52], further indicating that modulation of the CD4+ and CD8+ polyfunctionality scores may reduce the risk of HIV-1 infection, with CD8+ polyfunctionality playing a particularly important role. Notably, our analysis differs from the previous efforts in two ways: our estimates (i) are based on a formal causal model, which provides an alternative estimand to summarize relationships between immunogenic response and risk of HIV-1 infection, and (ii) leverage machine learning to allow the use of flexible modeling strategies while simultaneously delivering robust inference.

2.6 Discussion

A possible criticism of our approach is that, in the context of vaccines, the immune responses we consider may not be directly manipulable. Nevertheless, we believe the estimands that we consider pass the important litmus test question: "If we knew the value of the estimand, could we do something useful with it to advance science?" [59]. Knowledge of which immune responses may lead to the largest decrease in infection or disease incidence would advance vaccine science and stimulate new ideas for the next generation of vaccine research. Another challenge associated with our approach, as with many examples in causal inference, is selecting a scientifically meaningful intervention (i.e., modification of the exposure distribution). While we focused here on additive shifts for simplicity, more scrutiny of this choice is warranted in practice. Scientific context could provide some clues as to potentially meaningful shifts. For example, in the context of influenza vaccination, past studies have shown that repeated vaccinations may have a dulling effect on immune responses to new vaccines [161]. When such covariate data are available, they could be used to define an appropriate shift, where the proposed shift is lessened for individuals with many prior vaccinations.

Our analysis of the HVTN 505 trial could be improved in several respects. First, there was participant dropout observed in the trial, which our analysis ignored. A more robust analysis could leverage available covariate information to account for potentially informative missingness. Further, while we investigate the effect of altering post-vaccination immune responses on HIV-1 infection, the issue of interference could limit identifiability of our target causal effects. In trials conducted across geographically diverse sites or within short time frames, it may be reasonable to

assume that the potential protection conferred by immune response in a given unit would not alter the infection process in another unit, satisfying the lack of interference requirement for identifiability of the causal parameter of interest. Indeed, there is a growing body of work on relaxing this condition in causal inference [e.g., 85].

Beyond this issue, there are several other directions for potentially interesting extensions. First, when a range of shifts is of interest as in our example, we summarized linear trends using working marginal structural models. An alternative formulation could examine the stronger null hypothesis that $H_0 : \mathbb{E}Y_\delta = \mathbb{E}Y$, uniformly in δ. This is analogous to the hypothesis tests of Kennedy [91], which deals with shifted binary exposure distributions. There, the authors propose a test of this strong null hypothesis and describe methods for obtaining simultaneous confidence bands using the multiplier bootstrap. Second, it is of interest to extend our estimation strategy to other effects based on stochastic interventions, such as the population intervention (in)direct effects [35]. Extending our estimation strategy to such settings and its application in analyzing other vaccine efficacy trials will be the subject of future research.

2.7 Supplementary Material

Throughout our simulation experiments and data analyses, we rely on our `txshift` and `haldensify` `R` packages, both discussed in Chapter 5 and available at https://github.com/nhejazi/txshift and https://CRAN.R-project.org/package=haldensify, respectively. The `txshift` `R` package implements our proposed efficient estimators of the counterfactual mean outcome under a stochastic intervention (see Section 5.2 of Chapter 5), while our `haldensify` `R` package provides a nonparametric estimator of the generalized propensity score (see Section 5.4 of Chapter 5).

Algorithm for Efficient Targeted Minimum Loss Estimation

In Section 2.3, we introduced a novel algorithm for targeted minimum loss estimation with inverse probability of censoring weights. We formalize our procedure in Algorithm 3:

Algorithm 3: Efficient updating procedure for IPCW-TML estimation

Result: Updated sampling mechanism estimate $g^{\star}_{n,C}$ and updated outcome mechanism estimate $\overline{Q}^{\star}_{n,Y}$

Input :

Initial estimate of the sampling mechanism: $g_{n,C} \in [0, 1]$

Initial estimate of the outcome mechanism: $\overline{Q}_{n,Y} \in \mathbb{R}$

Estimate of the EIF pseudo-outcome regression: $G_n \in \mathbb{R}$

Estimate of the auxiliary covariate of the EIF: $H_n \in \mathbb{R}$

Observed indicators of the sampling mechanism: $C \in \{0, 1\}$

Initialize $g^{\star}_{n,C} \coloneqq 0$ and $\overline{Q}^{\star}_{n,Y} \coloneqq 0$;

while $g^{\star}_{n,C} = 0$ *and* $\overline{Q}^{\star}_{n,Y} = 0$ **do**

Define a working logistic regression model $\text{logit}(g_{n,C,\xi}) = \text{logit}(g_{n,C}) + \xi(G_n/g_{n,C}) : \xi \in \mathbb{R}$ and evaluate the MLE ξ_n of the parameter ξ, e.g., via iteratively reweighted least squares;

With the MLE ξ_n, extract predictions from this working model for the outcome, the conditional mean of C given $\{Y, W\}$, constructing the updated estimate $g^{\star}_{n,C} \coloneqq g_{n,C,\xi_n}$;

Define a weighted working logistic regression model $\text{logit}(\overline{Q}_{n,Y,\epsilon}) = \text{logit}(\overline{Q}_{n,Y}) + \epsilon H_n : \epsilon \in \mathbb{R}$, with weights $C_i/g^{\star}_{n,C}(Y_i, W_i)$, and construct the MLE ϵ_n of the model parameter ϵ;

With the MLE ϵ_n, construct the updated estimate of the outcome, the conditional mean of Y given $\{A, W\}$, by prediction to obtain $\overline{Q}^{\star}_{n,Y} \coloneqq \overline{Q}_{n,Y,\epsilon_n}$.

end

Output:

$g^{\star}_{n,C}$, an updated estimate of the sampling mechanism.

$\overline{Q}^{\star}_{n,Y}$, an updated estimate of the outcome mechanism.

Note that in the two working logistic regression models defined above, the inputs $g_{n,C}$ and $\overline{Q}_{n,Y}$ are both treated as offsets (known parameter value equal to one); thus, the working models are one-dimensional.

The outlined procedure includes two targeting steps. The first of these steps constructs an update of the initial estimator of the second-phase sampling probability, $g^{\star}_{n,C}$, based on the initial estimate of G_n. This step ensures that the revised estimate satisfies $\sum_{i=1}^{n}\{G_n(Y_i, W_i)/g^{\star}_{n,C}(Y_i, W_i)\}\{C_i - g^{\star}_{n,C}(Y_i, W_i)\} = 0$. in a single step when a universal least favorable submodel [174] is used, though an iterative procedure based on locally least favorable parametric submodels may be used to achieve the same result. In the second step, the updated outcome regression $\overline{Q}^{\star}_{n,Y}$ is generated based on the conditional density estimate $q_{n,A}$; the inclusion of weights in the regression ensures that $\sum_{i=1}^{n} C_i/g_{n,C}(Y_i, W_i)D^F_{n,i} = 0$.

Summarization via Working Marginal Structural Models

Estimation of $\psi_{0,\delta}$ for a single pre-specified shift δ may be unsatisfactory in some contexts, as it does not provide information concerning a dose-response relationship between exposure and outcome. Thus, to develop an understanding of a dose-response pattern in the context of stochastic interventions, it may be informative to estimate the counterfactual mean outcome across several values of δ. In the context of HVTN 505, we consider estimation of a grid of counterfactual means $\psi_0 = (\psi_{n,\delta_1}, \ldots, \psi_{n,\delta_K})$ and examine how the risk of HIV infection varies with choice of δ over a fixed grid, i.e., $\delta_k \in \{\delta_1, \ldots, \delta_K\}$. After estimating the counterfactual mean for each δ_k, a summary measure relating the stochastic interventions to the mean counterfactual outcomes may be constructed by projection onto a working marginal structural model (MSM). For example, we might consider a (possibly weighted) least-squares projection on the linear working model $m_\beta(\delta) = \beta_0 + \beta_1\delta$, in which case the parameter β_1 corresponds to the linear trend in mean counterfactual outcomes as a function of the δ_k.

More generally, we can define $\beta(\delta) = \text{argmin}_{\beta\in\mathbb{R}^d} \sum_{\delta\in\{\delta_1,\ldots,\delta_K\}} h(\delta)\{\psi_{0,\delta} - m_\beta(\delta)\}^2$, for a user-selected weight function $h(\delta)$. We note that adjustment of the weight function, as well as the functional form of $m_\beta(\delta)$, allow for a wide variety of working models to be considered. Alternatively, $\beta(\delta)$ can be viewed as the solution of

$$0 = U(\beta, \psi) = \sum_{\delta\in\{\delta_1,\ldots,\delta_K\}} h(\delta)\frac{d}{d\beta}m_\beta(\delta)\{\psi_{0,\delta} - m_\beta(\delta)\}.$$

The goal is to make statistical inference on the parameter β. We note that this approach does not assume a linear dose-response curve, but rather uses a working model to summarize the relationship between exposure and outcome [111]. This approach is distinct from that of Haneuse and Rotnitzky [68], whose proposal involving MSMs pertains specifically to parametric models.

To estimate β, we assume access to the TML or one-step estimates $\psi_n = (\psi_{n,\delta_1}, \ldots, \psi_{n,\delta_K})$ for each δ_k. The estimate β_n of β is the solution in β of the equation $0 = U(\beta, \psi_n)$. To derive the limit distribution of β_n, let $D_{0,\psi}$ denote a vector whose k^{th} entry is the EIF associated with parameter ψ_{0,δ_k}. The delta method implies that the influence function of β_n is $D_\beta = [-\frac{d}{d\beta}U(\beta,\psi_0)^{-1}]\frac{d}{d\psi_0}U(\beta,\psi_0)D_{\psi_0}$, and that $n^{1/2}(\beta_n - \beta)$ converges in distribution to a mean-zero Gaussian random variable with variance $\Sigma = \mathbb{E}_{P_0}\{D_\beta(O)^2\}$. The empirical covariance matrix of $D_{0,\psi}$ evaluated at nuisance parameter estimates serves to estimate Σ.

Proof of Theorem 1

We now examine a proof of the theorem establishing conditions for the weak convergence of our efficient estimators. Building upon Section 2.2, note that the full data parameter may be expressed as a mapping $\Psi^F : \mathcal{M}^X \to \mathbb{R}$ and that $\Psi^F(P_0^X) \equiv \Psi^F(\overline{Q}_{0,Y})$, since the parameter mapping depends on P_0^X only through the functional $\overline{Q}_{0,Y}$. We recall that the EIF $D^F(\overline{Q}_{0,Y}, g_{0,A})$ coincides with the canonical gradient of the parameter mapping $\Psi^F : \mathcal{M}^X \to \mathbb{R}$, since a regular asymptotically linear estimator with influence function equal to the canonical gradient is asymptotically efficient [14, 177]. Note further that the observed data parameter is defined such that $\Psi(P_0) \equiv \Psi^F(P_0^X)$, where the observed data parameter mapping $\Psi : \mathcal{M} \to \mathbb{R}$ is pathwise differentiable at a distribution P in the statistical model with a gradient given by the EIF:

$$D(G_0, g_{0,C}, D^F(\overline{Q}_{0,Y}, q_{0,A}))(o) = \frac{C}{g_{0,C}(y,w)} D^F(\overline{Q}_{0,Y}, q_{0,A})(x) - \frac{G_0(y,w)}{g_{0,C}(y,w)}(C - g_{0,C}(y,w)) \, .$$

The class of all gradients of Ψ at P is given by $\{D(G_0, g_{0,C}, D^F(P^X)) : D^F(P^X)\}$ where $D^F(P^X)$ varies over all gradients of the full data parameter Ψ^F at distributions $P^X \in \mathcal{M}^X$. As D^F varies, G_0 also necessarily varies since it is defined as the conditional mean of D^F given $\{C = 1, Y, W\}$. In particular, if the full data model $\mathcal{M}^X$ is nonparametric, then there is only one full data gradient, which is the canonical gradient (or EIF) of Ψ at P.

In the sequel, let $\|f\|_2 = \mathbb{E}\{f(O)^2\}^{1/2}$ denote the $L^2(P_0)$ norm of a P_0-measurable function f, define $\widetilde{G}_0 := \mathbb{E}_{P_0}[D^F(\overline{Q}^\star_{n,Y}, q_{n,A})(O) \mid C = 1, Y, W]$, and let G_n be the estimate of $\widetilde{G}_0$. An exact characterization of the second-order remainder for the full data parameter $\Psi^F(P^X) - \Psi^F(P_0^X)$ is given by

$$R_2^F(\overline{Q}_{n,Y}, q_{n,A}, \overline{Q}_{0,Y}, q_{0,A}) := \Psi^F(\overline{Q}_{n,Y}) - \Psi^F(\overline{Q}_{0,Y}) + \mathbb{E}_{P_0^X}[D^F(\overline{Q}_{n,Y}, q_{n,A})]$$

while the exact second-order remainder for the observed data parameter $\Psi(P) - \Psi(P_0)$ is analogously defined

$$R_2(P, P_0) := \Psi(P) - \Psi(P_0) + \mathbb{E}_{P_0}[D(G_n, g_{n,C}, D^F(\overline{Q}_{n,Y}, q_{n,A}))].$$

Combining these definitions, the exact second-order remainder for the observed data parameter may be expressed in terms of the second-order remainder of its full data counterpart:

$$R_2(P, P_0) = R_2^F(\overline{Q}_{n,Y}, q_{n,A}, \overline{Q}_{0,Y}, q_{0,A}) + \mathbb{E}_{P_0}\left[\left(\frac{g_{n,C} - g_{0,C}}{g_{n,C}}\right)(G_n - \widetilde{G}_0)\right].$$

Assume the following conditions:

Assumption 1. $\mathbb{E}_{P_n} D(G_n, g^\star_{n,C}, D^F(\overline{Q}^\star_{n,Y}, q_{n,A})) = 0$.

Assumption 2. $g_{0,C} > \zeta > 0$ *and* $g^\star_{n,C} > \zeta$ *with probability tending to 1 for some* $\zeta > 0$.

Assumption 3. $\|G_n - \widetilde{G}_0\|_{P_0} = o_P(n^{-1/4})$ *and* $\|g^\star_{n,C} - g_{0,C}\|_{P_0} = o_P(n^{-1/4})$.

Assumption 4. $R_2^F(\overline{Q}^\star_{n,Y}, q_{n,A}, \overline{Q}_{0,Y}, q_{0,A}) = o_P(n^{-1/2})$.

Assumption 5. $\|D(G_n, g^\star_{n,C}, D^F(\overline{Q}^\star_{n,Y}, q_{n,A})) - D(G_0, g_{0,C}, D^F(\overline{Q}_{0,Y}, q_{0,A}))\|_{P_0} = o_P(1)$.

Assumption 6. *Let* $\mathcal{F}_v^\star(M)$ *be the class of cadlag functions* f *on a cube* $[0, \tau] \subset \mathbb{R}^d$ *(for some integer* d*), for which the sectional variation norm* $\|f\|_v^\star$ *is bounded by a universal constant* $M < \infty$*. Assume that* $D(G_n, g^\star_{n,C}, D^F(\overline{Q}^\star_{n,Y}, q_{n,A})) \in \mathcal{F}_v^\star(M)$ *with probability tending to 1 (n.b., the definition* $\mathcal{F}_v^\star(M)$ *can be replaced by any Donsker class).*

Proof [Theorem 1: asymptotic linearity and efficiency of the TML estimator $\psi^\star_{n,\delta}$] Under conditions 1–6, we have $\mathbb{E}_{P_n} D(G_n, g^\star_{n,C}, D^F(\overline{Q}^\star_{n,Y}, q_{n,A})) = o_P(n^{-1/2})$; moreover, by definition of $R_2(P, P_0)$:

$$\begin{aligned}\Psi^F(\overline{Q}^\star_{n,Y}) - \Psi^F(\overline{Q}_{0,Y}) = &- \mathbb{E}_{P_0}[D(G_n, g^\star_{n,C}, D^F(\overline{Q}^\star_{n,Y}, q_{n,A}))] \\ &+ R_2^F(\overline{Q}^\star_{n,Y}, q_{n,A}, \overline{Q}_{0,Y}, q_{0,A}) + \mathbb{E}_{P_0}\left[\left(\frac{g^\star_{n,C} - g_{0,C}}{g^\star_{n,C}}\right)(G_n - \widetilde{G}_0)\right].\end{aligned}$$

Combining with condition 1, we have

$$\begin{aligned}\Psi^F(\overline{Q}^\star_{n,Y}) - \Psi^F(\overline{Q}_{0,Y}) = &\mathbb{E}_{P_n}[D(G_n, g^\star_{n,C}, D^F(\overline{Q}^\star_{n,Y}, q_{n,A}))] - \mathbb{E}_{P_0}[D(G_n, g^\star_{n,C}, D^F(\overline{Q}^\star_{n,Y}, q_{n,A}))] \\ &+ R_2^F(\overline{Q}^\star_{n,Y}, q_{n,A}, \overline{Q}_{0,Y}, q_{0,A}) + \mathbb{E}_{P_0}\left[\left(\frac{g^\star_{n,C} - g_{0,C}}{g^\star_{n,C}}\right)(G_n - \widetilde{G}_0)\right]\end{aligned}$$

The sum of the first two terms equals $\mathbb{E}_{P_n}[D(G_0, g^\star_{0,C}, D^F(\overline{Q}^\star_{0,Y}, q_{0,A})(O)] + o_P(n^{-1/2})$ as implied by conditions 5 and 6. Condition 4 ensures the third term equals $o_P(n^{-1/2})$. Conditions 2

and 3 imply that the fourth term equals $o_P(n^{-1/2})$, which completes the proof. An analogous proof holds for the one-step estimator $\psi^+_{n,\delta}$ when the initial estimates $\overline{Q}_{n,Y}$ and $g_{n,C}$ are used instead of their revised counterparts. Here, we do not require condition 1, as our proposed estimation procedure guarantees that it will be attained. □

Results of Additional Simulation Studies

Simulation #1b: Comparing Estimator Variants under Shifts $\delta = -0.5$ and $\delta = 0$

In the results reported in Section 2.4, for our first simulation study under the shift $\delta = 0.5$, we noted excellent performance of our proposed estimator variants under several standard metrics, including $\sqrt{n}$-bias, n-MSE, and the coverage of confidence intervals. To further assess the quality of performance of our augmented estimators, we examine the same six estimator variants under the shifts $\delta \in \{-0.5, 0\}$. Details of the simulation study have been previously described in Section 2.4. As before, results are reported based on aggregation across 1000 repetitions. The results of these numerical investigations are reported in Figures 7 and 8.

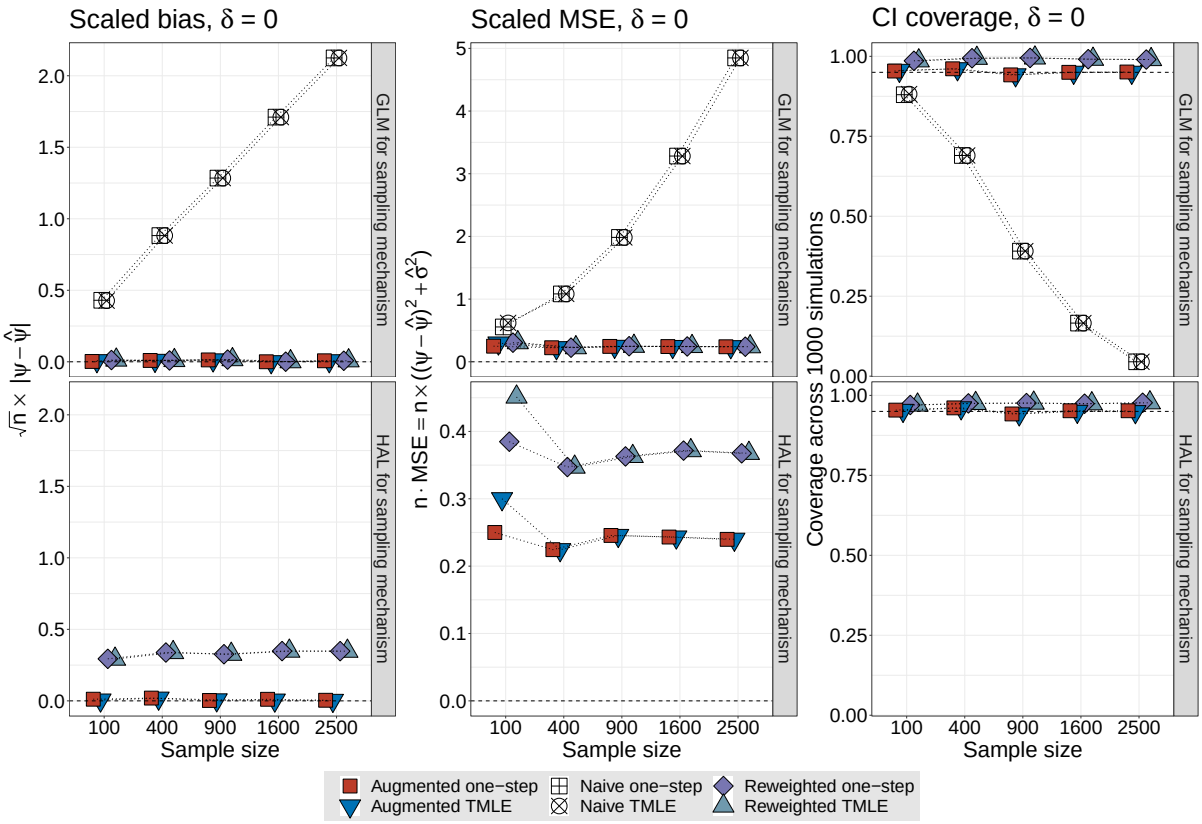

Figure 7: Results of numerical simulations comparing six estimation strategies for $\psi_{0,\delta}$ for $\delta = 0$.

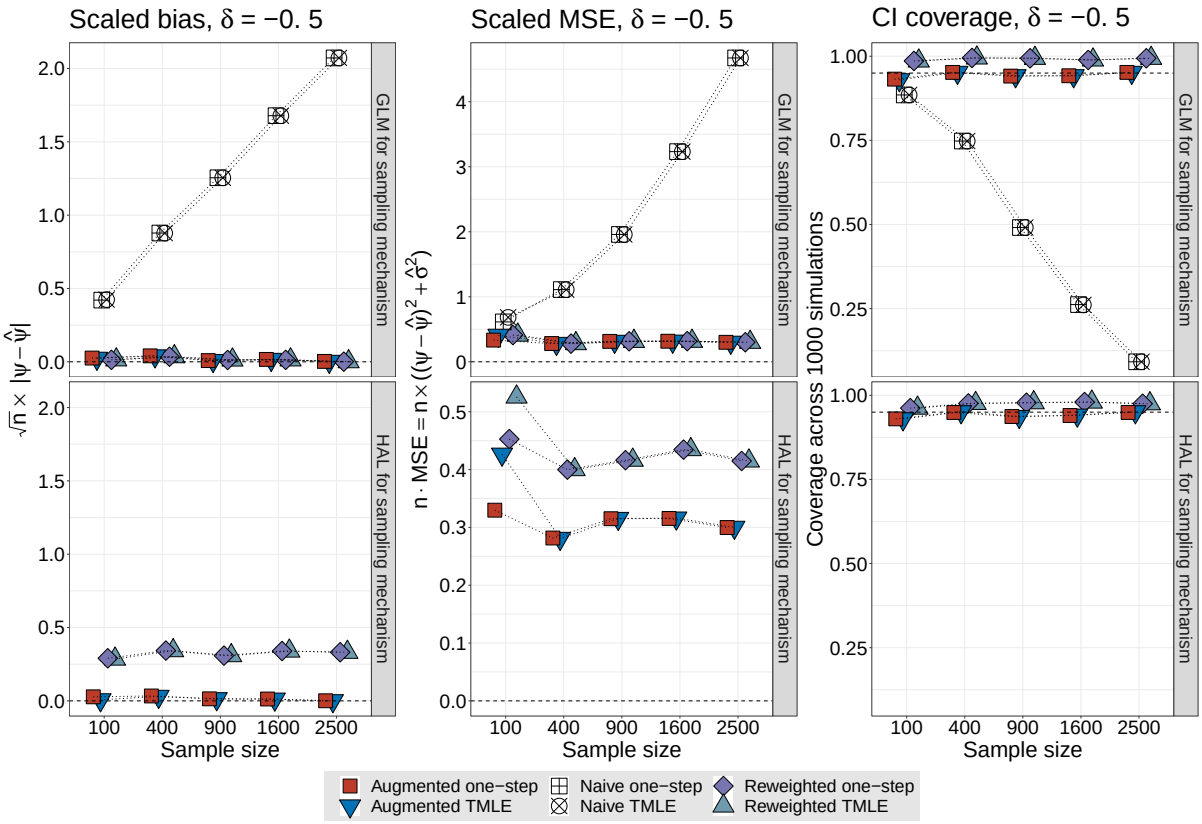

Figure 8: Results of numerical simulations comparing six estimation strategies for $\psi_{0,\delta}$ for $\delta = -0.5$.

Both the reweighted estimators of Rose and van der Laan [143] and our augmented estimators display the expected level of performance when the sampling mechanism is estimated via a correctly specified parametric model, standing out against the performance of their unadjusted counterparts. As in the case of $\delta = 0.5$, the reweighted estimators display coverage exceeding the desired 95% level, while their augmented analogs cover at exactly the nominal level. This suggests again that the reweighted estimators exhibit an inflated variance relative to that of our augmented estimators. The lower panel of each figure visualizes differences in the performance of the estimators when the sampling mechanism is estimated flexibly via HAL. These results reveal a significant discrepancy in the performance of the reweighted and augmented estimators, with our augmented one-step and TML estimators outperforming their reweighted counterparts in terms of $\sqrt{n}$-bias, n-MSE, and coverage. In this second case, we note that the TML estimators appear to exhibit a small degree of estimation instability at $n = 100$, displaying larger n-MSE in both the reweighted and augmented variants. We conjecture that this performance is due to an instability induced by the targeting procedure — in practice, this could be ameliorated by alterations to the

convergence criterion. Overall, the results of these numerical investigations do not differ substantially from those presented in Section 2.4, establishing that our augmented estimators improve upon alternative estimation strategies when nonparametric estimation of $g_{0,C}$ is performed.

Simulation #2a: Comparing estimators in a Setting Inspired by the HVTN 505 Trial

For use in real data analysis, we examine only our augmented one-step and TML estimators. We used the HVTN data to calibrate the following data-generating mechanism:

$$\begin{aligned}
W_1 &\sim \text{Normal}(26.6, 5.7); W_2 \sim \text{Poisson}(40); W_3 \sim \text{Bern}(0.4); W_4 \sim \text{Bern}(0.3) \\
A \mid W &\sim \text{Normal}(-1.37 + 0.004W_1 + 0.015W_2 + 0.05W_3 + 0.25W_4, 0.2^2) \\
Y \mid A, W &\sim \text{Bern}\left(\text{expit}(-2.9 - 0.0013W_1 - 0.0016W_2 + 0.0678W_3 + 0.039W_4 - 0.033A)\right) \\
C \mid Y, W &\sim \begin{cases} \text{Bern}\left(\text{expit}(-2.45 - 0.027W_1 + 0.012W_2 + 0.39W_3 + 0.166W_4)\right), & Y = 0 \\ 1, & Y = 1 \end{cases}.
\end{aligned}$$

Here, each of the structural equations were generated by fitting parametric linear or logistic models for $\mathbb{E}[A \mid W]$, $\mathbb{E}[Y \mid A, W]$ and $\mathbb{E}[C \mid Y = 0, W]$, the means of the CD4+ immunogenic marker, HIV-1 infection risk at month 24, and probability of inclusion in the second-phase sample, respectively. Meanwhile, the forms of $W_1, \ldots W_4$ were based on examination of the empirical distributions of the relevant baseline covariates. Specifically, with respect to the data from the HVTN 505 trial, W_1 mimics BMI, W_2 is based on participants' age, W_3 is a binarized clinical behavioral risk score for HIV-1 infection, and W_4 behaves as the binarized race/ethnicity. For consistency with the observed rate of HIV infection in the HVTN 505 trial, the outcome was made to have a relatively rare event rate, with $\mathbb{P}(Y = 1 \mid A, W) \approx 0.059$. We considered a setting where we observed $n = 1400$ i.i.d. observations, approximately matching the sample size of the vaccinated arm in HVTN 505. Estimator performance was assessed and reported by aggregating across 1000 repetitions. Under this data-generating mechanism, the true parameter values were approximated as $\psi_{0,\delta} = \{0.0627, 0.0617, 0.0609, 0.0598, 0.0589, 0.0580, 0.0571, 0.0561, 0.0554\}$ for $\delta \in \{-2.0, -1.5, -1.0, -0.5, 0.0, 0.5, 1.0, 1.5, 2.0\}$, respectively. An analogous setting, in which the effect of exposure on the outcome was removed, yielded similar results.

The proposed estimators were constructed by using the highly adaptive lasso to estimate the sampling mechanism $g_{n,C}$, the exposure mechanism $q_{n,A}$, the outcome mechanism $\overline{Q}_{n,Y}$, and the pseudo-outcome regression G_n. We compared the proposed one-step and TML estimators in terms of their bias, MSE, and coverage of 95% confidence intervals, summarizing the results in Figure 9.

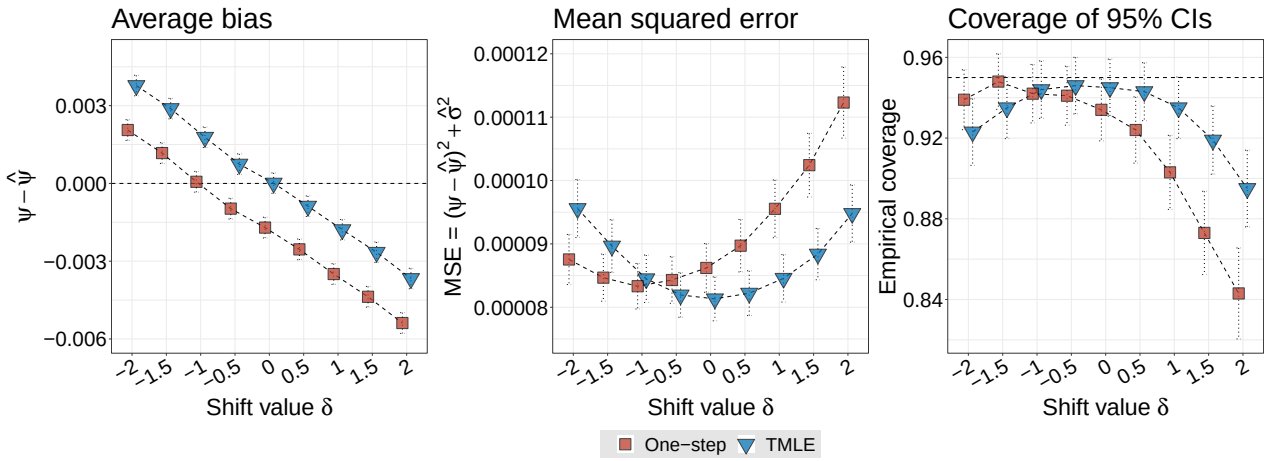

Figure 9: Results of numerical simulations comparing our two proposed estimators of $\psi_{0,\delta}$ for a grid of δ, across 1000 Monte Carlo simulations at $n = 1400$.

Inspection of the bias and MSE indicates that both of our proposed estimators display adequate performance, with small finite-sample bias and mean squared error. In terms of bias, the TML estimator outperforms the one-step at $\delta \geq -0.5$ while the one-step provides better performance at $\delta \leq -0.5$. Given the exceedingly small scale of the bias, we conclude this to be a particularity of this data-generating mechanism, not to be used as a guiding principle in practice. The bias appears to dominate the MSE, with the parabolic forms of the MSE curves having their respective minima at points at which each of the estimators is unbiased. Here, the two estimators achieve comparable performance at $\delta \leq 0$ but the TML estimator outperforms the one-step at other values of δ. Similarly, in terms of empirical coverage, both estimators provide coverage near the nominal rate for $\delta \leq 0.5$ but the performance of the TML estimator suffers less at larger δ. Importantly, we note that coverage at the nominal rate is only to be expected asymptotically and is not guarateed by theory in the finite-sample setting presently under consideration. From these numerical investigations, we concluded that our augmented estimators are both well-suited to estimating $\psi_{0,\delta}$ in the context of a re-analysis of data from the HVTN 505 trial.

Simulation #2b: Comparing estimators in a Setting Inspired by the HVTN 505 Trial, with No Treatment Effect

To further assess the performance of our augmented estimators in a scenario like the HVTN 505 trial, we replace the structural equation for the outcome Y with a draw from the Bernoulli distribution parameterized as $\text{Bern}(p = \text{expit}(-2.8 - 0.0013W_1 - 0.0016W_2 + 0.0678W_3 + 0.039W_4))$ to achieve a setting in which there is no effect of the treatment on the outcome. In this case, the

outcome process is relatively rare, with $\mathbb{P}(Y = 1 \mid A, W) \approx 0.053$. The structural equations for other components of the observed data O are unaltered. In this setting, the true parameter value was approximated to be $\psi_{0,\delta} = 0.0526$ regardless of the value of δ. We present the results of assessing our augmented estimators in Figure 10.

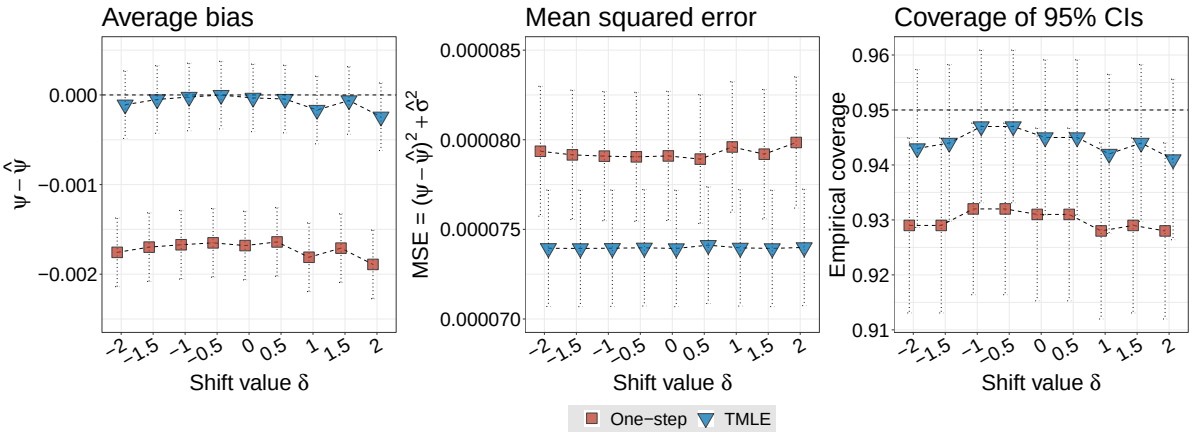

Figure 10: Results of numerical simulations comparing our two proposed estimators of $\psi_{0,\delta}$ for a grid of δ, across 1000 Monte Carlo simulations at $n = 1400$.

As the ground truth of the effect of shifting the post-vaccination activity of the CD4+ and CD8+ immunogenic markers on the risk of HIV-1 infection is unknown in the HVTN 505 trial, we assess our estimators in this scenario so as to be sure of there performance when no effect of treatment is present. Estimation of all nuisance parameters is performed using exactly the same techniques outlined previously in Section 2.7.

In terms of bias and MSE, our proposed estimators display adequate performance. With respect to both metrics, the TML estimator outperforms the one-step uniformly in δ, though both estimators display extremely low bias and MSE. In terms of the coverage of 95% confidence intervals, the TML estimator again outperforms the one-step estimator, though only very slightly. Unlike the results presented in Section 2.7, the performance of the estimators, in terms of all three metrics, appears stable across δ, providing further evidence that the phenomenon appearing in that numerical study was a particularity of the effect of A on Y under this data-generating mechanism. The improved performance of the TML estimator over the one-step estimator is in line with prior demonstrations of the enhanced finite-sample performance of TML estimators [179]. As with the numerical investigations presented in Section 2.7, these results suggest that our augmented estimators will perform well enough to allow accurate estimation of $\psi_{0,\delta}$ when applied to data from the HVTN 505 trial.

Super Learner Ensemble Models for $\overline{Q}_{n,Y}$ in the HVTN 505 Data Analysis

As noted in Section 2.5, for both the CD4+ and CD8+ analyses, the estimated outcome mechanism $\overline{Q}_{n,Y}$ was constructed from an ensemble model based on the super learner algorithm [176]. The cross-validation selector that forms the basis of the super learner has been shown to exhibit unique theoretical guarantees, including asymptotic equivalence to the oracle selector [171, 172, 183], that make its use preferable over other ensemble learning approaches.

A rich library of candidate classification algorithms was considered in the super learner ensemble model for $\overline{Q}_{n,Y}$. These included ℓ_1-penalized lasso regression [163, 53]; ℓ_2-penalized ridge regression [164, 83, 53]; three elastic net regressions weighting the ℓ_1 penalty at $\alpha \in \{0.25, 0.50, 0.75\}$ and the ℓ_2 penaly at $(1 - \alpha)$ [202, 53]; random forests [16] with 50, 100, and 500 trees based on its implementation in the `ranger` `R` package [194]; extreme gradient boosted trees with 20, 50, 100, and 300 fitting iterations [24]; multivariate adaptive polynomial spline regression [97, 157]; multivariate adaptive regression splines [55]; generalized linear models with Bayesian priors on parameters; a multilayer perceptron [145]; and the highly adaptive lasso [167, 11, 30]. The implementation of the super learner algorithm in the `sl3` `R` package [31] was used, and weights assigned to each learning algorithm by the super learner are given in Tables 2.1 and 2.2 for the CD4+ and CD8+ analyses, respectively.

Table 2.1: Weights and risk estimates assigned to each individual learning algorithm in the ensemble model for $\overline{Q}_{n,Y}$ used in the reported re-analysis of the CD4+ immunogenic marker.

Learner	Weight	Min. Fold Risk	Mean CV-Risk	Max. Fold Risk
Ridge (ℓ_2 penalized)	0.147	0.015	0.036	0.052
Lasso (ℓ_1 penalized)	0.000	0.015	0.036	0.052
Elastic net ($\alpha = 0.25$)	0.116	0.015	0.036	0.051
Elastic net ($\alpha = 0.50$)	0.000	0.015	0.036	0.051
Elastic net ($\alpha = 0.75$)	0.181	0.015	0.036	0.051
Random forest (50 trees)	0.000	0.062	0.097	0.173
Random forest (100 trees)	0.000	0.050	0.093	0.153
Random forest (500 trees)	0.000	0.061	0.093	0.158
xgboost(20 iterations)	0.000	0.012	0.072	0.165
xgboost(50 iterations)	0.000	0.012	0.080	0.181
xgboost(100 iterations)	0.010	0.013	0.088	0.192
xgboost(500 iterations)	0.000	0.012	0.098	0.204
Highly adaptive lasso (default)	0.014	0.064	0.074	0.084
Highly adaptive lasso (custom)	0.000	0.066	0.075	0.084
Multivariate regression splines	0.000	0.050	0.086	0.131
Polynomial spline regression	0.208	0.015	0.036	0.053
Multilayer perceptron network	0.000	0.015	0.037	0.055
GLM with Bayesian priors	0.323	0.015	0.036	0.051
Super Learner	1.000	—	—	—

In the super learner ensemble model for the outcome regression in the CD4+ analysis, the three best learning algorithms were a GLM with Bayesian priors on parameter estimates, a polynomial spline regression model, and an elastic net regression model that favored the ℓ_1 (lasso) penalty over the ℓ_2 (ridge) penalty. Another variant of elastic net regression, which favored the ℓ_2 penalty over the ℓ_1 penalty, and ridge regression were also given nontrivial weights in the ensemble model. A variant of extreme gradient boosting and the highly adaptive lasso received low weights, while all other candidate algorithms in the library were assigned weights of zero.

Table 2.2: Weights and risk estimates assigned to each individual learning algorithm in the ensemble model for $\overline{Q}_{n,Y}$ used in the reported re-analysis of the CD8+ immunogenic marker.

Learner	Weight	Min. Fold Risk	Mean CV-Risk	Max. Fold Risk
Ridge (ℓ_2 penalized)	0.161	0.013	0.037	0.075
Lasso (ℓ_1 penalized)	0.161	0.011	0.037	0.075
Elastic net ($\alpha = 0.25$)	0.003	0.012	0.037	0.075
Elastic net ($\alpha = 0.50$)	0.000	0.014	0.037	0.076
Elastic net ($\alpha = 0.75$)	0.131	0.014	0.037	0.074
Random forest (50 trees)	0.090	0.053	0.088	0.129
Random forest (100 trees)	0.055	0.048	0.089	0.136
Random forest (500 trees)	0.119	0.049	0.088	0.127
xgboost(20 iterations)	0.000	0.043	0.064	0.112
xgboost(50 iterations)	0.000	0.036	0.074	0.128
xgboost (100 iterations	0.000	0.031	0.076	0.134
xgboost (300 iterations)	0.000	0.029	0.086	0.146
Highly adaptive lasso (default)	0.000	0.046	0.078	0.115
Highly adaptive lasso (custom)	0.000	0.044	0.078	0.132
Multivariate regression splines	0.000	0.029	0.100	0.159
Polynomial spline regression	0.000	0.015	0.040	0.080
Multilayer perceptron network	0.067	0.007	0.040	0.085
GLM with Bayesian priors	0.214	0.016	0.037	0.073
Super Learner	1.000	—	—	—

In the CD8+ analysis, the three best learning algorithms, chosen by the super learner ensemble model for the outcome regression, were a GLM with Bayesian priors on parameter estimates, ridge regression, and lasso regression. Other algorithms that were assigned nontrivial weights included an elastic net regression model that favored the ℓ_1 (lasso) penalty over the ℓ_2 (ridge) penalty and a random forest with 500 trees. A variant of elastic net regression, random forests with 50 and 100 trees, and a multilayer perceptron all received low weights, while all other candidate algorithms in the library were assigned weights of zero.

Chapter 3

Stochastic Interventional Vaccine Efficacy

3.1 Introduction

The core ideas of Chapter 2 can form a novel approach to studying immune correlates of protection — those immunologic markers *causally* antagonistic to the process of infection [128]. In vaccine efficacy trials of infectious diseases, such analyses can aid in developing a more nuanced understanding of the differing roles that immunologic markers can play in impacting vaccine efficacy and, beyond this, elucidate the mechanism by which the activities of these markers may afford protection. This analytic framework quantifies vaccine efficacy as the effect attributable to shifting (upwards or downwards) the immune response distribution (i.e., immunologic marker activity) in vaccinees [78], revealing the complex interplay between vaccination, immunologic marker activity, and infection.

To formalize, let us denote by the random variable $O = (W, A, S, Y)$ the data collected on a single individual in a randomized vaccine efficacy trial, where W are clinically relevant baseline risk factors for infection (e.g., age, body mass index), A is the randomized assignment to placebo or vaccine, S is the immune response activity of an antibody of interest, and Y is an indicator of infection. Throughout, we assume that S is the scalar-valued activity of a particular antibody, as quantified by an established immunoassay, and is a candidate immune correlate of protection. In measuring S, we further assume that biological material (e.g., drawn blood) for evaluating the activity of the immunologic marker is taken at an *a priori*-specificed time post-vaccination. Since such trials often measure the time-to-infection, the outcome process is generally a composite time-to-event quantity $\{\tilde{T} = \min(T_F, T_C), \Delta = \mathbb{I}(T_F < T_C)\}$, where T_F and T_C are the (mutually unobservable) failure and censoring times, respectively, and Δ is simply the indicator of observed failure. We simplify this to $Y \coloneqq \mathbb{I}(\Delta = 1)$ (i.e., observed infection) by the end of the trial.

Leveraging the framework developed in Chapter 2, we formulate and evaluate vaccine efficacy

parameters in the context of efficacy trials of the vaccines produced to counteract the COVID-19 pandemic. The central goal of this and related statistical analyses [e.g., 10, 57] is to derive reliable, parsimonious surrogate endpoints [131, 58] based on the immunologic marker activity measured by a given immunoassay, effectively narrowing the set of candidate immune correlates of protection and curbing the time and resources consumed by vaccine efficacy trials. Alternative techniques and shared details of the data analytic approach are outlined in the immune correlates statistical analysis plan of the COVID-19 Vaccine Prevention Network (CoVPN) [61]. Each of outlined analyses is implemented in the `R` programming language [133], all publicly available at `https://github.com/CoVPN/correlates_reporting`, which incorporates version control and continuous integration for automated code checking and analysis report generation.

3.2 Formulating Vaccine Efficacy Parameters

Taking the outcome of interest Y to be the indicator of a COVID-19 disease endpoint of interest by a pre-specified time (e.g., $Y \in \{0, 1\}$ by Day 57 post-vaccination), we consider the counterfactual outcome $Y(a, s)$ generated by a hypothetical intervention setting both the randomized vaccination assignment (i.e., $A = a$) and the immunologic marker activity (at the specified timepoint) S to a random draw from an analyst-specified distribution. Consider the shift δ to be a hypothetical change in the standardized response activity of the immunologic marker S in question. In particular, we may conceive of the effect on risk of a given COVID-19 endpoint of a controlled intervention shifting the distribution of an immunologic response by δ units, for externally specified values of δ. Such interventions on vaccine-induced immunologic marker activity can be viewed as the hypothetical results of potential changes to the candidate vaccine, for example, change in dose or vaccine re-formulation. As the immunologic marker activity at $\delta = 0$ corresponds to that induced by the curent vaccine, we can consider counterfactual scenarios in which changes to the vaccine result in relatively heightened (if $\delta > 0$) or muted (if $\delta < 0$) immune response.

To query the counterfactual risk of the COVID-19 endpoint of interest under the hypothetical modified vaccine, that is, the vaccine inducing immune response $S + \delta$ for $\delta \in \mathbb{R}$, we naturally consider the mean of the counterfactual outcomes of the form $Y(1, S(1) + \delta)$, corresponding to the risk in vaccinees receiving the hypothetical vaccine. A similar approach, based on the controlled direct effect [10], evaluates the effect of an intervention that sets $S = s$ statically, thereby assuming that it is possible to set the post-intervention immune response value s for *all individuals in the population*. Unfortunately, this rather stringent assumption may be unrealistic when s is large and there exist subpopulations with within which the modified vaccine fails to elicit a strongly immunogenic response. The stochastic interventional approach presently described makes a far

laxer assumption on the intervention: The intervention need only shift immune responses relative to the observed value for a given individual, allowing for individual-specific (or subpopulation-specific) changes in vaccine-induced immunogenicity.

Under standard identification assumptions [37, 78], such as no unmeasured confounding and positivity, generally required for all causal analyses, the counterfactual risk $\mathbb{E}[Y(1, S(1) + \delta)]$ is identified by

$$\mathbb{E}[\mathsf{P}(Y = 1 \mid A = 1, S = S + \delta, W = w) \mid A = 1, W] \,. \tag{3.1}$$

By examining this quantity across a range of feasible δ values provides insight into the relative contribution of a given immunologic response marker in preventing the manifestation of the endpoint of interest. Noting that $\mathsf{P}(Y(0) = 1) = \mathsf{P}(Y = 1 \mid A = 0)$ (in view of vaccine versus placebo randomization, as given in [57]) and that this quantity may be estimated in the same way as for the controlled vaccine efficacy analyses, we define stochastic interventional vaccine efficacy (SVE) as

$$\text{SVE}(\delta) = 1 - \frac{\mathbb{E}[\mathsf{P}(Y = 1 \mid A = 1, S = S + \delta, W = w) \mid A = 1, W]}{\mathsf{P}(Y(0) = 1)} \,. \tag{3.2}$$

3.3 Considerations for Statistical Estimation

Hejazi et al. [78] proposed nonparametric estimators that rely on estimates of the outcome regression and the conditional density of the immune response in vaccinated participants. Their estimators efficiently account for two-phase sampling of immune responses and are implemented in the `txshift` package [73] for the `R` language and environment for statistical computing [133], freely available through both GitHub at `https://github.com/nhejazi/txshift` and the Comprehensive `R` Archive Network at `https://CRAN.R-project.org/package=txshift`.

To assess vaccine efficacy against COVID-19 endpoints, we apply these estimators to several immunologic markers measured at Day 57, controlling for a common set of baseline risk factors in the interest of alignment with other CoVPN analyses. For further details on the immunologic markers and risk factors, as well as key details on study design, we refer the interested reader to the comprehensive statistical analysis plan of Gilbert et al. [61]. Similar to the natural effects approach of Benkeser, Díaz, and Ran [10], our implementation leverages low-dimensional risk factors alongside parametric regression strategies and flexible conditional density estimation for endpoints with fewer than 100 observed cases (pooling across trial arms); however, more flexible statistical learning techniques are employed for modeling the outcome process for endpoints with a greater number of observed cases.

In particular, conditional density estimates of immune response markers are based principally on a nonparametric estimation strategy that constructs the conditional density through estimates

of the conditional hazard of the discretized immune response marker values [78, 74], as per Algorithm 2 of Chapter 1; this approach is an extension of the proposal of Díaz and van der Laan [39]. A Super Learner ensemble [176] of variants of this nonparametric conditional density estimator and the semiparametric location-scale conditional density estimation procedure discussed in Algorithm 1 of Chapter 1, as. implemented in the `sl3 R` package [31]. In settings with limited numbers of case endpoints, the outcome process is modeled as a Super Learner ensemble of a library of parametric regression techniques [per 66], while the algorithm library is augmented with flexible regression techniques — including, for example, lasso and ridge regression [163, 164, 83], elastic net regression [202, 53], random forests [16, 194], extreme gradient boosting machines [24], multivariate adaptive polynomial and regression splines [55, 157, 97], and the highly adaptive lasso [167, 11, 75, 30] — as the number of case endpoints grows. The choice of algorithm library is coordinated across the CoVPN correlates of protection analyses [61].

Output of the analyses will be presented as point and 95% confidence interval estimates of $\mathbb{E}[Y(1, S(1) + \delta)]$ and of $\text{SVE}(\delta)$ over the values of s for each of the Day 57 immunologic markers, for each of a range of δ spanning the interval $[-1, 1]$ on the standard unit scale for each immunologic marker. As with related analyses, in the context of data from real-world COVID-19 trials, these analyses are to be carried out only if diagnostics support plausibility of the positivity assumption. Notably, however, the positivity assumption for the stochastic interventional effects is unique. Where the positivity assumption for effects defined by static interventions requires a positive probability of treatment assignment across *all strata* defined by baseline factors (i.e., that a discretized immune response value be possible regardless of baseline factors), the positivity assumption of our effects is

$$s_i \in \mathcal{S} \implies s_i + \delta \in \mathcal{S} \mid A = 1, W = w$$

for all $w \in \mathcal{W}$ and $i = 1, \ldots n$. In particular, this positivity assumption does not require that the post-intervention exposure density, $q_{0,S}(S - \delta \mid A = 1, W)$, place mass across all strata defined by W. Instead, it requires that the post-intervention exposure mechanism be bounded, that is,

$$\mathsf{P}\{q_{0,S}(S - \delta \mid A = 1, W)/q_{0,S}(S \mid A = 1, W) > 0\} = 1,$$

which may be readily satisfied by a suitable choice of δ.

Importantly, the static intervention approach may require consideration of counterfactual variables that are scientifically unrealistic. Namely, it may be inconceivable to imagine a world where every participant exhibits high immune responses, given the phenotypic variability of participants' immune systems. This too may be resolved by considering an intervention indexed not by δ but by $\delta(W)$, that is, one in which the choice of the shift is itself a function of the baseline covariates W [78, 37, 68, 38].

3.4 Application to the COVID-19 Pandemic

We estimate the counterfactual mean of symptomatic COVID-19 infection under posited shifts in the measured activity levels of each of immunologic markers that are *candidate* mechanistic correlates of protection (mCoP), as defined by the aims of the CoVPN statistical analysis plan [61]. By shifting the *standardized* immunologic activity levels by standard unit shifts along the grid $\{-1, -0.5, 0, 0.5, 1\}$, we can assess the degree to which vaccines that modulate mCoP immunologic marker activity to these modified levels could mitigate symptomatic COVID-19 infection in terms of both counterfactual stochastic interventional risk and vaccine efficacy (VE). In the sequel, we demonstrate our approach using the Day 57 activity of the spike protein binding and pseudo-neutralizing antibodies.

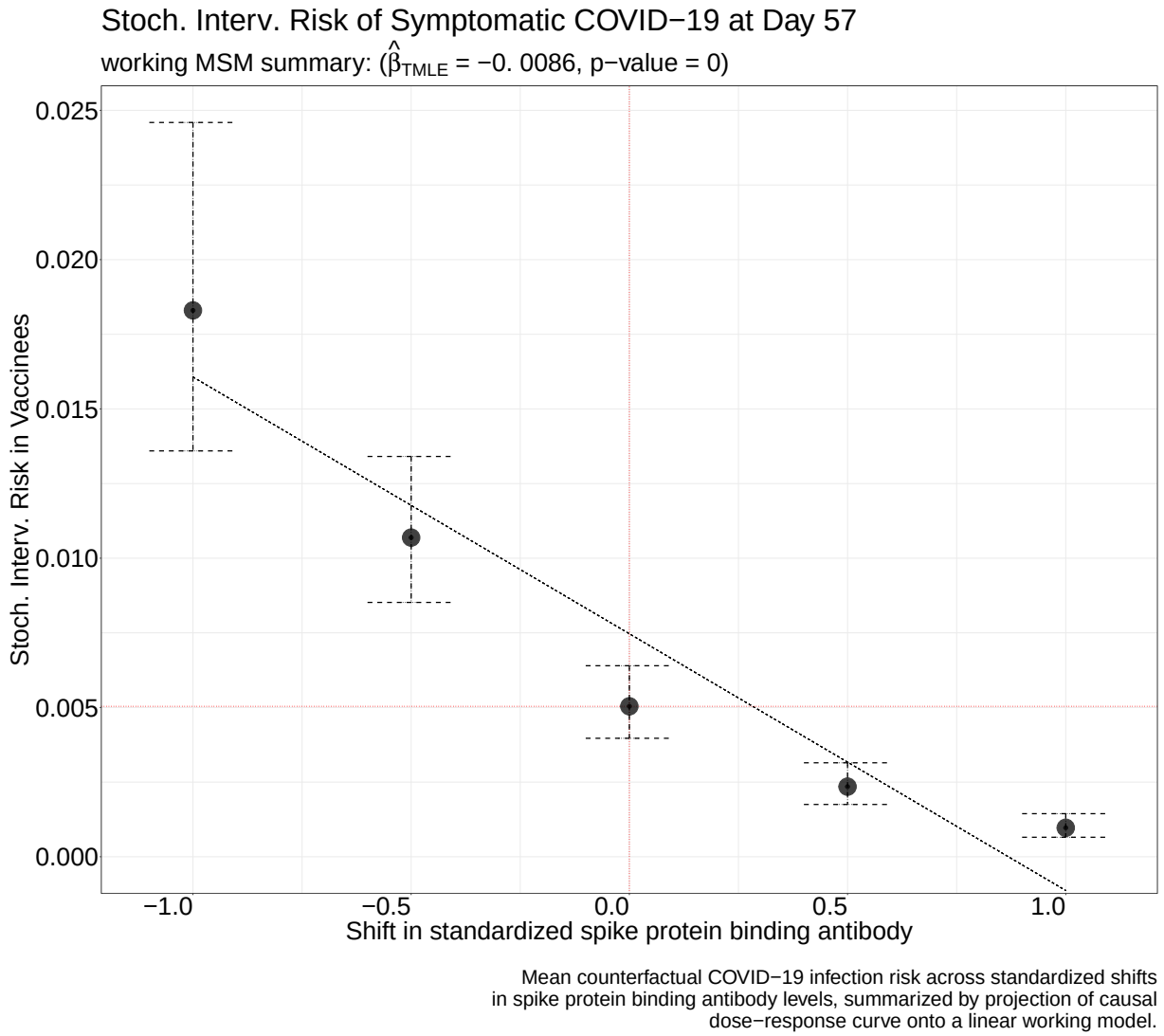

Figure 11: Stochastic interventional risk estimates, with confidence intervals, for the spike protein binding antibody at Day 57.

Estimation of the stochastic interventional risk for the spike protein antibody across several values of δ reveals a monotonic decrease in risk with increases in the activity of this immunologic marker. In particular, at $\delta = 0$, for the vaccine administered in the current efficacy trial, the estimated risk of symptomatic COVID-19 infection at Day 57 is 0.5%. For positive values of δ, reflecting increased activity of the spike protein antibody, the estimated risk of the adverse endpoint decreases towards zero. This suggests that improvements to the dosage or formulation of the current vaccine may be capable of improving its efficacy further still. Considering now negative values of δ, it appears that even moderate decreases in the modulation of this antibody marker can

significantly limit the efficacy of the vaccine against infection. For example, with $\delta = -0.5$, the estimated risk doubles to 1.00%; moreover, risk appears to grow sharply with further decreases in marker activity. To summarize the trend in the change in estimated risk across the grid in δ, we note that projection onto a working marginal structural model (MSM; as per Chapter 2) yields a linear form with slope $\hat{\beta}_{\text{TMLE}} = -0.0086$ and corresponding p-value of $p < 0.001$ for the hypothesis test of no trend (i.e., $H_0 : \beta = 0$ and $H_1 : \beta \neq 0$).

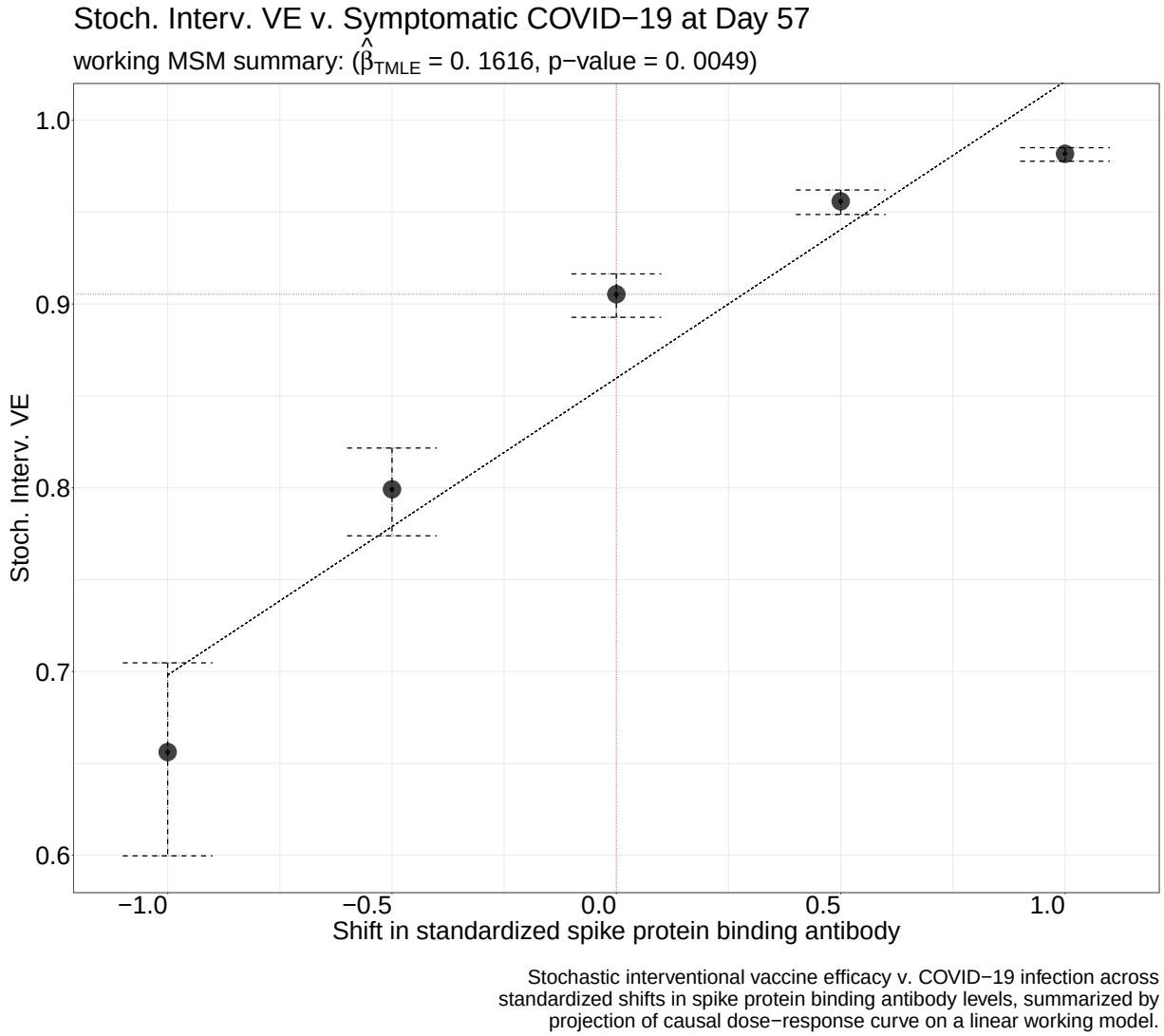

Figure 12: Stochastic interventional VE estimates, with confidence intervals, for the spike protein binding antibody at Day 57.

The evaluation of stochastic interventional VE is a process of re-scaling the corresponding

stochastic interventional risk estimates by the risk of infection in the placebo arm of the trial, as per equation (3.2). Accordingly, the estimated VE provides information similar to that provided by the risk estimates. In the case of the spike protein antibody, we find that the VE produced by the administered vaccine (i.e., at $\delta = 0$) is just over 90%. What's more, upwards shifts of the activity of this marker have moderate impacts on the estimated VE, with vaccine efficacy estimates of roughly 95% and 97% for $\delta = 0.5$ and $\delta = 1$, respectively. While this analysis suggests that reconstituting a future vaccine so as to specifically increase the activity of the spike protein antibody may lead to very limited increases in protection, the risk estimates at downwards shifts in its activity strongly suggest that all vaccines ought to seek to module this marker at the level at which the current vaccine does so. Specifically, a decrease of just a half standard unit (i.e., $\delta = -0.5$) leads to an estimated risk of 80%, while a decrease of a full standard unit ($\delta = -1$) yields a risk estimate of about 65% — 10% and 25% lower, respectively, than the risk estimate for the administered vaccine. Examination of how VE estimates vary along the grid in δ reveals a sharp increasing trend for the projection of the VE estimates onto a linear working MSM. The slope parameter of the MSM is estimated to be $\hat{\beta}_{\text{TMLE}} = 0.1616$ with a p-value of $p < 0.01$ for the hypothesis test of no trend.

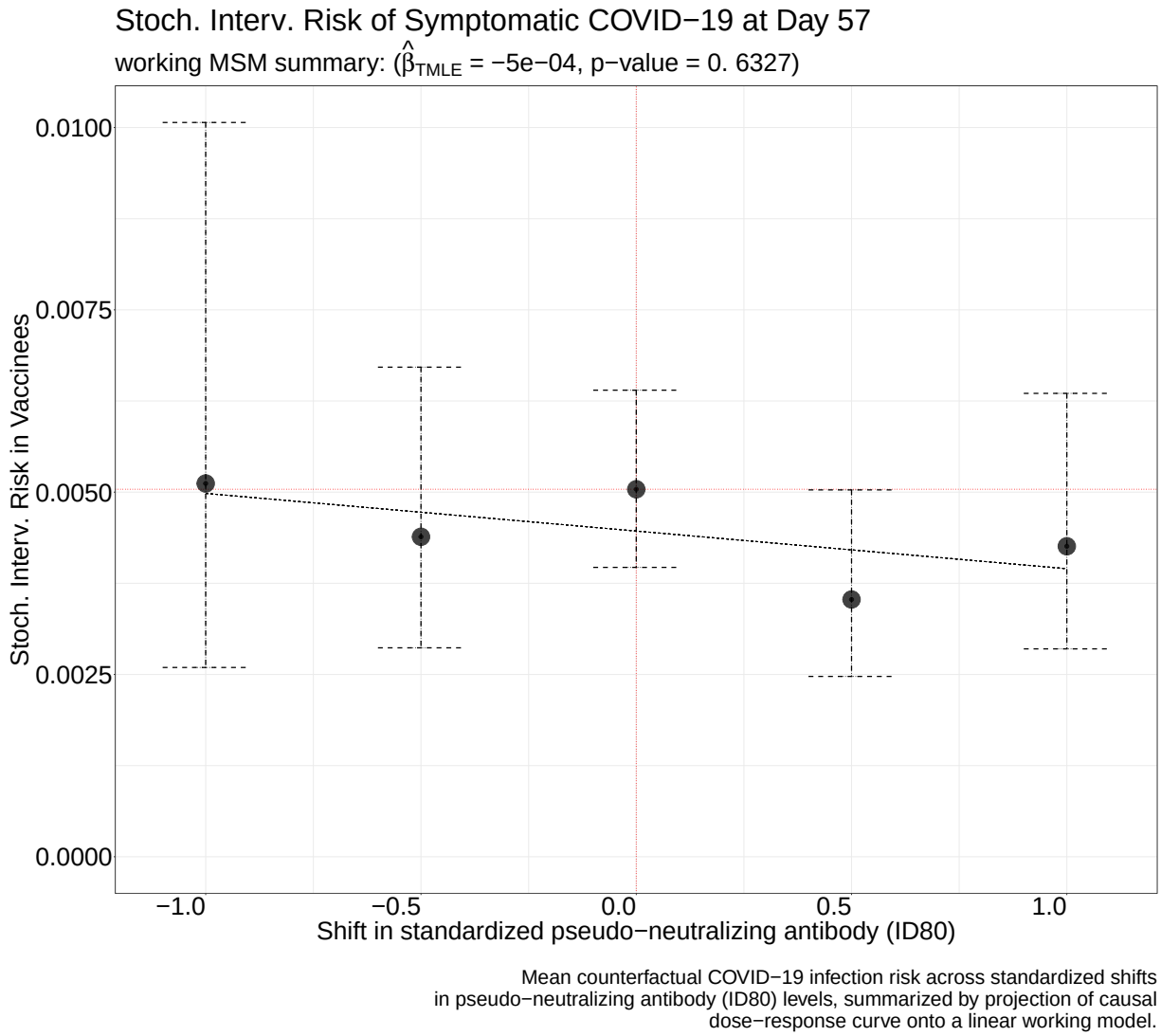

Figure 13: Stochastic interventional risk estimates, with confidence intervals, for the pseudo-neutralizing antibody at Day 57.

Estimation of the stochastic interventional risk for the pseudo-neutralizing antibody across the grid in δ reveals that the estimated risk is largely insensitive to hypothetical changes in the marker activity. To start, considering $\delta = 0$ (i.e., the activity of S induced by the currently administered vaccine), estimated risk of symptomatic COVID-19 infection at Day 57 is 0.5%. The estimated stochastic interventional risk lies close to this value for other values of δ, suggesting that the pseudo-neutralizing antibody may not be a suitable target for designing future vaccines to further curb the risk of symptomatic COVID-19 infection.

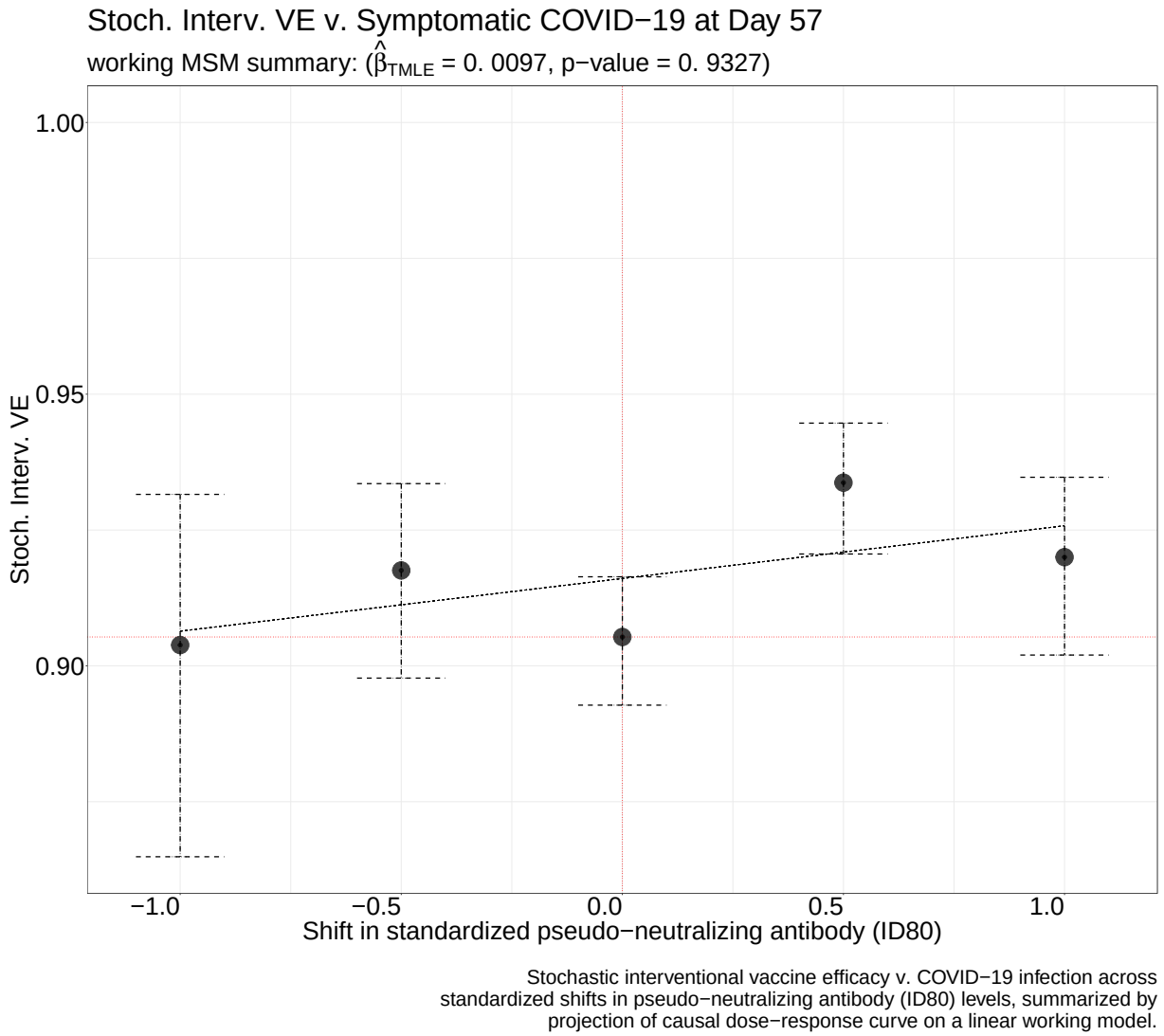

Figure 14: Stochastic interventional VE estimates, with confidence intervals, for the pseudo-neutralizing antibody at Day 57.

Similarly to the estimates of the stochastic interventional risk for shifting of the pseudo-neutralizing antibody, the stochastic VE estimates all lie within roughly 3% of the estimated VE at the null shift of $\delta = 0$. Examining the VE estimate at that shift, we note an efficacy of roughly 90%, with no sharp or consistent changes in VE estimates at upwards or downwards shifts of the activity of this marker. Consistent with the risk analyses, these VE estimates suggest the pseudo-neutralizing antibody to be an unpromising candidate for targeting by future vaccines.

Chapter 4

Stochastic Interventional Causal Mediation

Causal mediation analysis has historically been limited in two important ways: (i) a focus has traditionally been placed on binary exposures and static interventions, and (ii) direct and indirect effect decompositions have been pursued that are only identifiable in the absence of intermediate confounders affected by exposure. We present a theoretical study of an (in)direct effect decomposition of the population intervention effect, defined by stochastic interventions jointly applied to the exposure and mediators. In contrast to existing proposals, our causal effects can be evaluated regardless of whether a exposure is categorical or continuous and remain well-defined even in the presence of intermediate confounders affected by exposure. Our (in)direct effects are identifiable without a restrictive assumption on cross-world counterfactual independencies, allowing for substantive conclusions drawn from them to be validated in randomized controlled trials. Beyond the novel effects introduced, we provide a careful study of nonparametric efficiency theory relevant for the construction of flexible, multiply robust estimators of our (in)direct effects, while avoiding undue restrictions induced by assuming parametric models of nuisance parameter functionals. To complement our nonparametric estimation strategy, we introduce inferential techniques for constructing confidence intervals and hypothesis tests, and discuss open source software, the `medshift` `R` package, implementing the proposed methodology. Application of our (in)direct effects and their nonparametric estimators is illustrated using data from a comparative effectiveness trial examining the direct and indirect effects of pharmacological therapeutics on relapse to opioid use disorder.

4.1 Introduction

In myriad applications, one is often interested in the effect of an exposure on an outcome only through a particular pathway between the two. Indeed, efforts in defining and identifying such

path-specific effects have come to constitute a rich history in not only philosophy but also in the sciences of statistics, causal inference, epidemiology, economics, and psychology. In each of these disciplines, as well as in many others among the biomedical and social sciences, developing a mechanistic understanding of the complexities that admit representations as path-specific effects remains a central goal; examples include elucidating the biological mechanism by which a vaccine reduces infection risk [e.g., 29, 78], assessing the effect on preterm birth of maternal exposure to environmental toxins [e.g., 49], and ascertaining the effect of novel pharmacological therapies on substance abuse disorder relapse.

The latter serves as our motivating example as we consider how exposure to a buprenorphine dose schedule characterized by successive increases toward a maximum dose early in treatment (versus static dose) affects the risk of relapse to opioid use disorder, both directly and indirectly through mediating factors such as depression and pain. Developing a detailed mechanistic understanding of the process by which such therapeutics modulate intermediary states is necessarily a *causal* question — one central to designing and successively improving upon available therapies in a manner targeted towards the mitigation of the risk of substance abuse relapse. In comparative effectiveness trials of promising opioid use disorder therapeutics, detailed dissections of the complex neurological and psychiatric pathways involved in the development of addiction disorders is of clinical interest [98, 151]. The ability to define and evaluate causal effects along paths involving or avoiding mediating neuropsychiatric sequela would facilitate drug efficacy assessments; moreover, the ability to refine scientific conclusions based on statistical evidence through randomized controlled trials remains integral to furthering clinical progress.

To carefully study complex mediation relationships, a wealth of techniques rooted in statistical causal inference have been formulated. Path analysis [195, 196], perhaps the earliest example of such methodology, directly inspired the development of subsequent techniques that leveraged parametric structural equation models [e.g., 63, 6] for mediation analysis. More recently, the advent of modern frameworks and formalisms for causal inference, including nonparametric structural equation models, directed acyclic graphs, and their underlying do-calculus [116, 117], provided the necessary foundational tools to express causal mechanisms without reliance on more restrictive approaches tied to parametric modeling.

In tandem with the developments of Pearl [117], similar approaches spearheaded by Robins [136], Spirtes et al. [153], Dawid [34], and [134] allowed nonparametric formulations of mediation analysis and uncovered significant limitations of the earlier efforts focused on structural equation models [119, 87]. Recent applications of modern causal models have illustrated the failings of popular parametric modeling strategies [i.e., 6], in the presence of intermediate confounders of the mediator-outcome relationship [27]. Consequently, the usually implausible assumptions that underlie such restrictive structural equation models make these approaches of limited applicability

for the examination of complex phenomena in the biomedical, health, and social sciences.

Modern approaches to causal inference have allowed for significant advances over the methodology of traditional mediation analysis, overcoming the significant restrictions imposed by the use of parametric structural equation modeling. For example, Robins and Greenland [137] and Pearl [118], using distinct frameworks, provided equivalent nonparametric decompositions of the average treatment effect (for binary exposures) into the *natural* direct and indirect effects, which quantify all effects of the treatment on the outcome through paths avoiding the mediator and all paths involving the mediator, respectively. Such advances were not without their limitations, however. A key assumption of the nonparametric decomposition of the average treatment effect is the requirement of *cross-world* counterfactual independencies (i.e., the condition that counterfactuals indexed by distinct intervention assignments be independent). Unfortunately, such an assumption limits the scientific relevance of the natural (in)direct effects by making them unidentifiable in randomized trials, directly implying that corresponding scientific claims cannot be falsified through experimentation [129, 34, 140]. Importantly, such cross-world independencies are also unsatisfied in the presence of intermediate confounders affected by treatment [3, 160]. As such confounders are often present in practice, the natural (in)direct effects are of limited applicability.

A related thread of the literature has considered stochastic interventions, which generalize many intervention classes. For example, within this framework, static interventions result in post-intervention exposures that have degenerate distributions. Stock [155] first considered the estimation of the total effects of stochastic interventions, while many others [e.g., 139, 41, 162, 120, 154, 68, 36, 44, 198] provided careful studies that expanded the underlying theory of stochastic interventions and demonstrated their numerous applications. Uniquely, stochastic interventions can be applied to define causal effects of continuous-valued exposures, with an interpretation echoing that of regression adjustment. For example, Díaz and van der Laan [37] and Haneuse and Rotnitzky [68] described modified treatment policies, which assign post-intervention counterfactuals based on the natural value of the exposure; their methods were demonstrated in the context of increasing leisure physical activity in the elderly and reducing surgical time for non-small-cell lung cancer operations. Stochastic interventions have also successfully been applied to binary exposures: Kennedy [91] proposed incremental propensity score interventions and demonstrated their use in longitudinal studies in order to circumvent identifiability and estimation issues arising from positivity violations.

Contemporaneously, Díaz and Hejazi [35] proposed a decomposition of the total effect of stochastic interventions into the population intervention (in)direct effects, which are endowed with interpretations analogous to that of the natural (in)direct effects. Prior related attempts at the same [e.g., 189] introduced parametric modeling assumptions to lessen reliance on the assumption of cross-world counterfactual independencies, introducing flexibility at the cost of bias and re-

strictive assumptions on post-intervention distributions. In a similar vein, the stochastic (in)direct effects of Díaz and Hejazi [35] do not require cross-world counterfactual independencies but succeed in accommodating nonparametric estimation strategies. Consequently, these population intervention (in)direct effects may be estimated without restrictive assumptions and yield scientific results that can be tested through randomization of both the exposure and mediator. Despite these advances, the results of Díaz and Hejazi [35] suffer a serious shortcoming — that is, these effects lack identifiability in the presence of intermediate confounders, which affect both mediators and outcome and are themselves affected by the exposure. This incompatibility with intermediate confounding motivated the development of a new and promising family of *interventional* (in)direct effects [41, 188, 104, 190, 200, 152, 103, 113], which utilize joint static and stochastic interventions (applied to the exposure and mediators, respectively) to retain identifiability under such confounding. Until recently, nonparametric effect decompositions and efficiency theory were unavailable for this class of effects, though efforts by Daz et al. [42] and Benkeser [9] have sought to provide some remedy. While resolving the issues arising from requiring cross-world counterfactual independencies, these interventional (in)direct effects are limited by their lack of applicability beyond binary exposures.

In the present work, we outline a general framework encompassing many prior causal mediation analysis approaches, including the natural (in)direct effects, their interventional effect counterparts, and the stochastic (in)direct effects. Building upon the foundations laid by Díaz and Hejazi [35], the introduced class of mediation effects originate from combining the novel lines of inquiry established in the distinct literatures on stochastic interventions and the interventional effects; accordingly, we denote these *stochastic interventional (in)direct effects*. Our proposed class of effects are the first to simultaneously avoid the requirement of cross-world counterfactual independencies; leverage stochastic interventions to be applicable to binary, categorical, and continuous-valued exposures; and remain identifiable despite intermediate confounding. As such, our contributions apply to a broader class of exposures than the interventional effects [e.g., 42, 9] while generalizing stochastic (in)direct effects [e.g., 35] to accommodate the presence of intermediate confounders. While our robust and flexible causal mediation analysis framework subsumes prior classes of effect definitions, this is far from enough for the successful application of our proposed (in)direct effects. To this end, we develop novel efficiency theory and efficient nonparametric estimators of this broad new class of causal mediation parameters, within the frameworks of one-step [127, 14] and targeted minimum loss estimation [180, 179, 178]. These flexible estimators have desirable asymptotic properties even when nuisance parameter functionals are estimated via machine learning; moreover, they are endowed with a form of multiple robustness producing consistent point estimates under several configurations of nuisance parameter misspecification. Lastly, we provide implementations of our methodological advances in our free and open source `medshift` [76]

package, for the R language and environment for statistical computing [133].

4.2 Mediation Analysis for the Population Intervention Effect

Let A denote a continuous or categorical exposure variable, Y denote a continuous or binary outcome, Z denote mediator(s), W denote a vector of observed pre-exposure covariates, and L denote an intermediate (mediator-outcome) confounder affected by exposure. We formalize the causal inference problem via the nonparametric structural equation model (NPSEM):

$$\begin{aligned} W = f_W(U_W); A = f_A(W, U_A); L = f_L(A, W, U_L); \\ Z = f_Z(L, A, W, U_Z); Y = f_Y(Z, L, A, W, U_Y). \end{aligned} \tag{4.1}$$

In the NPSEM (4.1), $U = (U_W, U_A, U_L, U_Z, U_Y)$ is a vector of exogenous factors, and the functions f are assumed deterministic but unknown. This mechanistic model is assumed to generate the observed data O; it encodes several fundamental assumptions. First, an implicit temporal ordering $W \to A \to L \to Z \to Y$ is assumed. Second, each variable (i.e., $\{W, A, L, Z, Y\}$) is assumed to be generated from the corresponding deterministic function of the observed variables that precede it temporally, plus an exogenous variable denoted by U. Each exogenous variable is assumed to contain all unobserved causes of the corresponding observed variable. For a random variable X, let X_a denote the counterfactual outcome observed in a hypothetical world in which $\mathsf{P}(A = a) = 1$. For example, we have $L_a = f_L(a, W, U_L)$, $Z_a = f_Z(L_a, a, W, U_Z)$, and $Y_a = f_Y(Z_a, L_a, a, W, U_Y)$. Likewise, we let $Y_{a,z} = f_Y(z, L_a, a, W, U_Y)$ denote the value of the outcome in a hypothetical world where $\mathsf{P}(A = a, Z = z) = 1$. Figure 15 represents model (4.1) in terms of a directed acyclic graph (DAG).

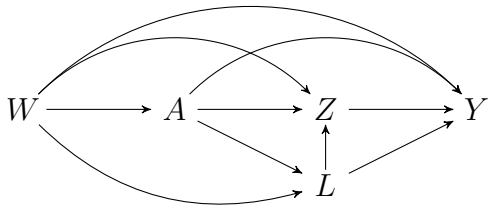

Figure 15: Directed Acyclic Graph of NPSEM (4.1).

Letting $O = (W, A, Z, L, Y)$ represent a random variable with distribution P, we denote by $O_1, \ldots, O_n$ a sample of n i.i.d. observations of O. We let $\mathsf{P}f = \int f(o)\mathrm{d}\mathsf{P}(o)$ for a given function $f(o)$. We use P_c to denote the joint distribution of (O, U), and let $\mathbb{E}$ and $\mathbb{E}_c$ denote corresponding

expectation operators. We use P_n to denote the empirical distribution of $O_1, \ldots, O_n$, and assume $\mathsf{P} \in \mathcal{M}$, where $\mathcal{M}$ is the nonparametric statistical model defined as all continuous densities on O with respect to a dominating measure ν. Let p denote the corresponding probability density function. We use $\mathsf{g}(a \mid w)$ and $\mathsf{e}(a \mid z, w)$ to denote the probability density function or the probability mass function of A conditional on $W = w$ and (Z, W), respectively; $\mathsf{m}(z, l, a, w)$ to denote the outcome regression function $\mathbb{E}(Y \mid Z = z, L = l, A = a, W = w)$. Let $\mathsf{g}(\cdot \mid w)$ and $\mathsf{e}(\cdot \mid z, w)$ be dominated by a measure $\kappa(a)$ (e.g., the counting measure for binary A and the Lebesgue measure for continuous A). We will use the parameterizations

$$\frac{\mathsf{p}(z \mid w)}{\mathsf{p}(z \mid a, w)} = \frac{\mathsf{g}(a \mid w)}{\mathsf{e}(a \mid z, w)}; \qquad \frac{\mathsf{p}(z \mid a, w)}{\mathsf{p}(z \mid l, a, w)} = \frac{\mathsf{p}(l \mid a, w)}{\mathsf{p}(l \mid z, a, w)} \tag{4.2}$$

in constructing our estimators, as such parameterizations allow for estimation and integration with respect to multivariate conditional densities on the mediator Z to be avoided. We use $\mathcal{W}$, $\mathcal{A}$, $\mathcal{Z}$, $\mathcal{L}$, and $\mathcal{Y}$ to denote the support of the corresponding random variables.

Causal effects are defined in terms of hypothetical interventions on the NPSEM (4.1). In particular, consider an intervention in which the structural equation corresponding to A is removed, with the treatment drawn instead from a user-specified distribution $g_\delta(a \mid w)$, which may itself depend on the natural exposure distribution and a user-specified parameter δ. Going forward, we let A_δ denote a draw from $g_\delta(a \mid w)$. Alternatively, such modifications can occasionally be described in terms of an intervention in which the structural equation corresponding to A is removed and the treatment is set equal to a hypothetical regime $d(A, W)$. Regime d depends on the treatment level A that would be assigned in the absence of the regime as well as on W. The latter intervention has been referred to as depending on the *natural value of treatment*, or as a *modified treatment policy* [68]. For such interventions, Haneuse and Rotnitzky [68] introduced the assumption of *piecewise smooth invertibility*, which ensures that the change of variable formula can be used when computing integrals over $\mathcal{A}$:

A6 (Piecewise smooth invertibility)**.** For each $w \in \mathcal{W}$, assume that the interval $\mathcal{I}(w) = (l(w,), u(w))$ may be partitioned into subintervals $\mathcal{I}_{\delta,j}(w) : j = 1, \ldots, J(w)$ such that $d(a, w)$ is equal to some $d_j(a, w)$ in $\mathcal{I}_{\delta,j}(w)$ and $d_j(\cdot, w)$ has inverse function $h_j(\cdot, w)$ with derivative $h'_j(\cdot, w)$.

Assumption A6 can be used to show that the intervention drawing A_δ from the post-intervention distribution $\mathsf{g}_\delta(a \mid w)$ can be interpreted on the individual level. Young, Hernán, and Robins [198] provide a discussion comparing and contrasting the interpretation and identification of these two interventions. Such stochastic interventions can be used to define the *population intervention effect (PIE)* of A on Y. To illustrate, consider continuous-valued A and assume the distribution of A

conditional on $W = w$ is supported in the interval $(l(w), u(w))$. Then, one may define

$$d(a, w) = \begin{cases} a - \delta & \text{if } a > l(w) + \delta \\ a & \text{if } a \leq l(w) + \delta, \end{cases} \tag{4.3}$$

where $0 < \delta < u(w)$ is an arbitrary prespecified value. We can alternatively define a tilted intervention distribution as

$$\mathsf{g}_\delta(a \mid w) = \frac{\exp(\delta a)\mathsf{g}(a \mid w)}{\int \exp(\delta a)\mathsf{g}(a \mid w)\mathrm{d}\kappa(a)}, \tag{4.4}$$

for $\delta \in \mathbb{R}$. Kennedy [91] proposed a form of exponential tilting (4.4) under the parameterization $\delta' = \exp(\delta)$, appropriate for incremental interventions on the propensity score for binary A. Díaz and Hejazi [35] provide a careful study of the interventions 4.3 and 4.4 in the context of mediation, introducing novel (in)direct effects and corresponding efficiency theory; however, their contributions assume the absence of intermediate confounding.

Stochastic Mediation Effects

[35] defined the (in)direct effect of A on Y in terms of a decomposition of the total effect of a stochastic intervention. In particular, the total effect $\mathbb{E}(Y - Y_{A_\delta})$ may be decomposed as the sum of the population intervention direct and indirect effects (PIDE; PIIE):

$$\begin{aligned} \text{PIDE} &= \mathbb{E}_c\{f_Y(Z, L, A, W, U_Y) - f_Y(Z, L_{A_\delta}, A_\delta, W, U_Y)\} \\ \text{PIIE} &= \mathbb{E}_c\{f_Y(Z, L_{A_\delta}, A_\delta, W, U_Y) - f_Y(Z_{A_\delta}, L_{A_\delta}, A_\delta, W, U_Y)\}. \end{aligned}$$

Upon inspection, the definitions above reveal that the direct effect measures the effect through paths *not* involving the mediator (i.e., $A \to Y$ and $A \to L \to Y$), whereas the indirect effect measures the effect through paths involving the mediator (i.e., $A \to Z \to Y$ and $A \to L \to Z \to Y$).

Unfortunately, the population intervention (in)direct effects are not generally identified in the presence of an intermediate confounder affected by treatment such as in the DAG in Figure (15) [35]. This is due to the dual role of L as a confounder of the relation between Z and Y, which requires adjustment, and a variable on the path from A to Y, which precludes adjustment. It is exactly this issue that the interventional effects [188] resolve, though their limitation to static interventions and binary exposures is too significant a limitation. Next, we present a solution to this complication using a joint stochastic intervention on the exposure A and mediator Z. We also show that the effects defined in this paper are a generalization of the effects of [35] in the sense that the former reduce to the latter in the absence of intermediate confounding.

Stochastic Interventional Mediation Effects

To introduce (in)direct effects robust to the presence of intermediate confounders, we draw upon ideas first outlined by [41], [126], and [175], all subsequently formalized by [188] and [190]. Owing to their definition in terms of stochastic interventions on the mediator, these (in)direct effects have been collectively termed *interventional effects*. We leverage two types of stochastic interventions: one on the treatment A, which defines the intervention of interest, and one on the mediator Z, which is used to achieve identifiability of the effects. Following the convention of the literature, we term stochastic interventions on the mediator Z *interventional*, while reserving the label of *stochastic* to refer only to interventions on the treatment A. To proceed, let G_δ denote a random draw from the distribution of Z_{A_δ} conditional on (A_δ, W), and let G denote a random draw from the distribution of Z conditional on (A, W). We consider the effect defined by $\psi_\delta = \mathbb{E}_c\{Y_{A,G} - Y_{A_\delta,G_\delta}\}$. Note that the effect ψ_δ is distinct from the effect considered by [35], which may be expressed $\mathbb{E}_c\{Y_{A,Z} - Y_{A_\delta,Z_\delta}\}$. The effect ψ_δ arises from fixing the mediator to a random value chosen from its distribution among all those with a particular treatment level, rather than fixing it to what it would have been under a particular (static) treatment. Defining the effect in this way aids in achieving an identifiable decomposition into direct and indirect effects. In particular, we may decompose this effect in terms of interventional stochastic *direct effects (DE)* and *indirect effects (IE)*:

$$\psi(\delta) = \overbrace{\mathbb{E}\{Y_{A,G} - Y_{A_\delta,G}\}}^{\text{DE}} + \overbrace{\mathbb{E}\{Y_{A_\delta,G} - Y_{A_\delta,G_\delta}\}}^{\text{IE}}. \tag{4.5}$$

Decomposition as the sum of direct and indirect effects affords an interpretation analogous to the corresponding standard decomposition of the average treatment effect into the natural direct and indirect effects [118]. In particular, the direct effect arises from drawing a counterfactual value of A from a post-intervention distribution while keeping the distribution of Z fixed. The indirect effect arises from replacing the distribution of Z with a candidate post-intervention distribution while holding A fixed. Our proposed stochastic interventional effects have an interpretation similar to the interventional effects of VanderWeele, Vansteelandt, and Robins [188]; moreover, while both effect definitions account for the presence of an intermediate confounder, our (in)direct effects utilize flexible, stochastic interventions on the exposure while those of VanderWeele, Vansteelandt, and Robins [188] are limited to static interventions on binary exposures. By generalizing the effect definitions of Díaz and Hejazi [35], our proposed (in)direct effects include, as special cases, the natural (in)direct effects (under a static intervention on binary A and no intermediate confounders L), the interventional (in)direct effects (under a static intervention on binary A and a stochastic intervention on Z, allowing intermediate confounders L), and the stochastic (in)direct effects (under a stochastic intervention on arbitrary-valued A and no intermediate confounders L).

Identification

To construct estimators of our proposed causal (in)direct effects, we turn to examining assumptions needed to estimate components of the post-intervention quantities corresponding to counterfactual variables of interest. Towards this end, we introduce the following identification assumptions:

A7 (Common support)**.** Assume $\text{supp}\{\mathsf{g}_\delta(\cdot \mid w)\} \subseteq \text{supp}\{\mathsf{g}(\cdot \mid w)\}$ for all $w \in \mathcal{W}$.

A8 (No unmeasured exposure-outcome confounder)**.** Assume $Y_{a,z} \perp\!\!\!\perp A \mid W$.

A9 (No unmeasured mediator-outcome confounder)**.** Assume $Y_{a,z} \perp\!\!\!\perp Z \mid (L, A, W)$.

A10 (No unmeasured exposure-mediator confounder)**.** Assume $Z_a \perp\!\!\!\perp A \mid W$.

Under these assumptions, we have the following identification results. A proof is available in the 4.8.

Theorem 2 (Identification)**.** *Define*

$$\theta_{1,\delta} = \int \mathsf{m}(z, l, a, w)\mathsf{p}(l \mid a, w)\mathsf{p}(z \mid a, w)\mathsf{g}_\delta(a \mid w)\mathsf{p}(w)\mathrm{d}\nu(a, z, l, w),$$
$$\theta_{2,\delta} = \int \mathsf{m}(z, l, a, w)\mathsf{p}(l \mid a, w)\mathsf{p}(z \mid w)\mathsf{g}_\delta(a \mid w)\mathsf{p}(w)\mathrm{d}\nu(a, z, l, w).$$

Under A7–A10, the direct effect $\psi_{D,\delta}$ and indirect effect $\psi_{I,\delta}$ (4.5) are identified, respectively, by

$$\begin{aligned} \psi_{D,\delta} &= \theta_{1,0} - \theta_{2,\delta} \\ \psi_{I,\delta} &= \theta_{2,\delta} - \theta_{1,\delta}. \end{aligned} \tag{4.6}$$

Assumption A8 states that, conditional on W, there is no unmeasured confounding of the relation between A and Y; assumption A10 states that conditional on W there is no unmeasured confounding of the relation between A and Z; and assumption A9 states that conditional on (W, A, L) there is no unmeasured confounding of the relation between Z and Y. These assumptions are standard in causal mediation analysis. In addition to these assumptions, standard mediation analyses [e.g., 188] require positivity assumptions on the treatment and mediation mechanisms. The stochastic intervention framework we adopt does not require such assumptions, as positivity can be arranged by definition of g_δ. For example, the interventions in expressions (4.3) and (4.4) satisfy assumption A7 by definition. The interested reader is encouraged to consult [91] and [35] for a discussion on this topic.

Another consequence of this identification result is that the definitions (4.6) reduce to the stochastic (in)direct effects of [35] in the absence of intermediate confounders L. Importantly, this implies that our estimators can be safely used in the absence of intermediate confounders;

furthermore, it implies that the corresponding estimates may be interpreted in terms of a decomposition of the population intervention effect $\mathbb{E}_c\{Y - Y_{A_\delta}\}$, which is arguably of more scientific interest than the interventional effect $\psi_\delta = \mathbb{E}_c\{Y_{A,G} - Y_{A_\delta,G_\delta}\}$.

As is clear from the definition (4.6), evaluation of $\psi_{\mathrm{D},\delta}$ and $\psi_{\mathrm{I},\delta}$ requires access to $\theta_{1,0}$, the population mean in the absence of any intervention on the treatment mechanism, as well as both of $\theta_{1,\delta}$ and $\theta_{2,\delta}$, which are based on the post-intervention treatment mechanism $\mathrm{g}_\delta(a \mid w)$. Consequently, we next turn our attention to developing efficiency theory for estimation of the statistical parameter $\theta_{j,\delta} : j = 1, 2$, which depends on the observed data distribution P.

4.3 Optimality Theory for Estimation of the Direct Effect

Thus far, we have discussed the decomposition of the effect of a stochastic intervention into direct and indirect effects and have provided identification results under under standard identifiability assumptions. We consider the development of efficiency theory for the estimation of $\theta_{1,\delta}$ and $\theta_{2,\delta}$ in the nonparametric model $\mathcal{M}$. To do so, we introduce the *efficient influence function* (EIF), which characterizes the asymptotic behavior of all regular and asymptotically linear estimators [14, 182]. Three common approaches exist for constructing local efficient estimators based on the EIF: (i) estimating equation [e.g., 177], (ii) one-step bias correction [e.g., 127, 14], and targeted minimum loss estimation [180, 179, 178].

As a consequence of its representation in terms of orthogonal score equations, the EIF allows the construction of consistent estimators of the target parameter even when certain components of its distribution are inconsistently estimated. Thirdly, second-order bias terms may be derived from asymptotic analysis of estimators constructed based on the EIF — often, these estimators require slow convergence rates (e.g., $n^{-1/4}$) for the nuisance parameters involved. This latter property enables the use of flexible, data adaptive regression techniques in estimating these quantities.

For simplicity, we focus on the case of a binary intermediate confounder L, though our general approach requires only that either L or Z be low-dimensional. In Theorem 3, we present the EIF for a general stochastic intervention. Although the components of the EIF associated with (Y, Z, L, W) are the same, the component associated with the model for the distribution of A must be computed on a case-by-case basis, that is, for each intervention of interest. Lemmas 3 and 4 present such components for modified treatment policies satisfying assumption A6 and for exponential tilting, respectively. In theorem 3 below, we present a representation of the EIF that avoids the computation of multivariate integrals over Z. To introduce the EIF, we define the following

auxiliary nuisance parameters:

$$\begin{aligned}
\mathsf{u}(z,a,w) &= \int \mathsf{m}(z,l,a,w)\mathrm{d}\mathsf{P}(l \mid a,w); \qquad \bar{\mathsf{u}}(a,w) = \int \mathsf{u}(z,a,w)\mathrm{d}\mathsf{P}(z \mid a,w) \\
\mathsf{v}(l,a,w) &= \int \mathsf{m}(z,l,a,w)\mathrm{d}\mathsf{P}(z \mid a,w); \qquad \bar{\mathsf{v}}(a,w) = \int \mathsf{v}(l,a,w)\mathrm{d}\mathsf{P}(l \mid a,w) \\
\mathsf{s}(l,a,w) &= \int \mathsf{m}(z,l,a,w)\mathrm{d}\mathsf{P}(z \mid w); \qquad \bar{\mathsf{s}}(a,w) = \int \mathsf{s}(l,a,w)\mathrm{d}\mathsf{P}(l \mid a,w)
\end{aligned} \tag{4.7}$$

Proofs for the following results are detailed in Section 4.8.

Theorem 3 (Efficient influence functions)**.**

$$H^1_{\mathsf{P},\delta}(a,z,l,w) = \frac{\mathsf{g}_\delta(a \mid w)}{\mathsf{g}(a \mid w)} \frac{\mathsf{p}(z \mid a,w)}{\mathsf{p}(z \mid a,l,w)}; \quad H^2_{\mathsf{P},\delta}(a,z,l,w) = \frac{\mathsf{g}_\delta(a \mid w)}{\mathsf{g}(a \mid w)} \frac{\mathsf{p}(z \mid w)}{\mathsf{p}(z \mid a,l,w)} \tag{4.8}$$

The efficient influence functions for $\theta_{j,\delta} : j = 1,2$ in the nonparametric model are equal to $D^j_{\mathsf{P},\delta}(o) - \theta_{j,\delta}$, where $D^j_{\mathsf{P},\delta}(o) = S^j_{\mathsf{P},\delta}(o) + S^{j,A}_{\mathsf{P},\delta}(o)$ and

$$\begin{aligned}
S^1_{\mathsf{P},\delta}(o) &= H^1_{\mathsf{P},\delta}(a,z,l,w)\{y - \mathsf{m}(z,l,a,w)\} && (4.9)\\
&+ \frac{\mathsf{g}_\delta(a \mid w)}{\mathsf{g}(a \mid w)}\Big[\mathsf{v}(l,a,w) - \bar{\mathsf{v}}(a,w) + \mathsf{u}(z,a,w) - \bar{\mathsf{u}}(a,w)\Big] && (4.10)\\
&+ \int \bar{\mathsf{u}}(a,w)\mathsf{g}_\delta(a \mid w)\mathrm{d}\kappa(a) \\
S^2_{\mathsf{P},\delta}(o) &= H^2_{\mathsf{P},\delta}(a,z,l,w)\{y - \mathsf{m}(z,l,a,w)\} && (4.11)\\
&+ \frac{\mathsf{g}_\delta(a \mid w)}{\mathsf{g}(a \mid w)}\{\mathsf{s}(l,a,w) - \bar{\mathsf{s}}(a,w)\} && (4.12)\\
&+ \int \mathsf{u}(z,a,w)\mathsf{g}_\delta(a \mid w)\mathrm{d}\kappa(a),
\end{aligned}$$

and $S^{1,A}_{\mathsf{P},\delta}(o)$, $S^{2,A}_{\mathsf{P},\delta}(o)$ are the respective efficient score functions of the model for $g(a \mid w)$.

An immediate consequence of Theorem 3 is that, in a randomized trial, $S^{j,A}_{\mathsf{P},\delta}(o) = 0$ for $j = 1,2$; however, even in such trials, covariate adjustment can improve the efficiency of the resultant estimator [177]. We now present the efficient scores $S^{j,A}_{\mathsf{P},\delta}(o)$ for modified treatment policies and exponentially tilted stochastic interventions. To do so, we define the parameter $\mathsf{q}(a,w) = \int \mathsf{u}(z,a,w)\mathrm{d}\mathsf{P}(z \mid w)$.

Lemma 3 (Modified treatment policies)**.** *If the modified treatment policy $d(A,W)$ satisfies assumption A6, then*

$$\begin{aligned}
S^{1,A}_{\mathsf{P},\delta}(o) &= \bar{\mathsf{u}}(d(a,w),w) - \int \bar{\mathsf{u}}(d(a,w),w)\mathsf{g}(a \mid w)\mathrm{d}\kappa(a) \\
S^{2,A}_{\mathsf{P},\delta}(o) &= \mathsf{q}(d(a,w),w) - \int \mathsf{q}(d(a,w),w)\mathsf{g}(a \mid w)\mathrm{d}\kappa(a).
\end{aligned}$$

Lemma 4 (Exponential tilt)**.** *If the stochastic intervention is the exponential tilt (4.4), then*

$$S^{1,A}_{\mathsf{P},\delta}(o) = \frac{\mathsf{g}_\delta(a \mid w)}{\mathsf{g}(a \mid w)} \left\{ \bar{\mathsf{u}}(a,w) - \int \bar{\mathsf{u}}(a,w)\mathsf{g}_\delta(a \mid w)\mathrm{d}\kappa(a) \right\} \tag{4.13}$$

$$S^{2,A}_{\mathsf{P},\delta}(o) = \frac{\mathsf{g}_\delta(a \mid w)}{\mathsf{g}(a \mid w)} \left\{ \mathsf{q}(a,w) - \int \mathsf{q}(a,w)\mathsf{g}_\delta(a \mid w)\mathrm{d}\kappa(a) \right\} \tag{4.14}$$

For binary treatments, the EIF corresponding to the incremental propensity score intervention may be simplified as per the following corollary.

Corollary 1 (Efficient influence function for incremental propensity score interventions)**.** *Let A take values on $\{0,1\}$, and let the exponentially tilted intervention $g_{\delta,0}(1 \mid W)$ be based on (4.4) under the parameterization $\delta' = \exp(\delta)$. Then, the EIF of Lemma 4 may be simplified as follows. Define the nuisance parameters*

$$\begin{aligned} \mathsf{q}^1(w) &= \bar{\mathsf{u}}(1,w) - \bar{\mathsf{u}}(0,w), \\ \mathsf{q}^2(w) &= \mathbb{E}\left\{ \mathsf{u}(Z,1,W) - \mathsf{u}(Z,0,W) \mid W = w \right\}, \end{aligned} \tag{4.15}$$

Then

$$S^{j,A}_{\eta,\delta}(o) = \frac{\delta \mathsf{q}^j(w)\{a - \mathsf{g}(1 \mid w)\}}{\{\delta \mathsf{g}(1 \mid w) + 1 - \mathsf{g}(1 \mid w)\}^2}.$$

In contrast to the efficient influence function for the interventional (in)direct effects [42], the contribution of the treatment process to the EIF for the stochastic interventional effects is non-zero. This is a direct consequence of the fact that the parameter of interest depends on g; moreover, this implies that the efficiency bound in observational studies differs from the efficiency bound in randomized trials. Thus, it is not generally possible to obtain estimating equations robust to inconsistent estimation of g. Such robustness will only be possible if the stochastic intervention is also a modified treatment policy satisfying assumption A6.

The form of Theorem 3 makes it clear that estimation of multivariate or continuous conditional density functions on the mediators Z or intermediate confounders L, as well as integrals with respect to these density functions, is generally necessary for computation of the EIF. This poses a significant challenge from the perspective of estimation, due to both the curse of dimensionality and the practical computational complexity inherent in solving multivariate numerical integrals. A simplification is possible when either either of Z or L is low-dimensional; this is achieved by reparameterizing the densities as conditional expectations (or low-dimensional conditional densities) that take other nuisance parameters as pseudo-outcomes is possible. To demonstrate, we assume L is univariate (e.g., binary as in our illustrative application), though similar parameterizations may be achieved if Z is low-dimensional. In cases where L or Z is low-dimensional, our proposed reparameterizations allow for the conditional density to be estimated via appropriate semiparametric estimators [e.g., 39].

Lemma 5 (Low-dimensional L and Z)**.** *If L is low-dimensional (e.g., binary and univariate) and Z is multivariate, we can choose a representation of v, s, and $\bar{\mathsf{u}}$ in terms of conditional expectations in order to facilitate their estimation. Denote $\mathsf{b}(l \mid a, w)$ and $\mathsf{d}(l \mid z, a, w)$ the probability that $L = l \in \{0, 1\}$ conditional on (A, W) and (Z, A, W), respectively. Then, using (4.2), we have*

$$\begin{aligned}
\mathsf{v}(l, a, w) &= \mathbb{E}\left[\mathsf{m}(z, l, a, w)\frac{\mathsf{b}(L \mid A, W)}{\mathsf{d}(L \mid Z, A, W)} \,\middle|\, L = l, A = a, W = w\right], \\
\mathsf{s}(l, a, w) &= \mathbb{E}\left[\mathsf{m}(z, l, a, w)\frac{\mathsf{b}(L \mid A, W)}{\mathsf{d}(L \mid Z, A, W)}\frac{\mathsf{g}(A \mid W)}{\mathsf{e}(A \mid Z, W)} \,\middle|\, L = l, A = a, W = w\right], \\
\bar{\mathsf{u}}(a, w) &= \mathbb{E}\left[\mathsf{u}(Z, A, W) \,\middle|\, A = a, W = w\right].
\end{aligned} \tag{4.16}$$

Likewise,

$$H^1_{\mathsf{P},\delta}(a, z, l, w) = \frac{\mathsf{g}_\delta(a \mid w)}{\mathsf{g}(a \mid w)}\frac{\mathsf{b}(l \mid a, w)}{\mathsf{d}(l \mid z, a, w)}; \quad H^2_{\mathsf{P},\delta}(a, z, l, w) = \frac{\mathsf{g}_\delta(a \mid w)}{\mathsf{e}(a \mid z, w)}\frac{\mathsf{b}(l \mid a, w)}{\mathsf{d}(l \mid z, a, w)},$$

and

$$\mathsf{q}(a, w) = \mathbb{E}\left\{\frac{\mathsf{g}(A \mid W)}{\mathsf{e}(A \mid Z, W)}\mathsf{u}(Z, A, W) \mid A = a, W = w\right\}.$$

Analogous representations may be constructed for $\bar{\mathsf{v}}$, $\bar{\mathsf{s}}$, and u based on the parameterizations (4.2) if L is multivariate and Z is of low dimension. We note, however, that at least one of Z or L must be of small dimensionality so that its density may be estimated and integrals over its range may be computed with ease.

In what follows, we assume L is univariate, denote $\eta = (\mathsf{m}, \mathsf{g}, \mathsf{b}, \bar{\mathsf{u}}, \mathsf{v}, \mathsf{d}, \mathsf{e}, \mathsf{s}, \mathsf{q})$ and let $D^j_{\mathsf{P},\delta}(o) = D^j_{\eta,\delta}(o)$. The choice of parameterization in Lemma 5 has important consequences for the purpose of estimation, as it helps to bypass estimation of the (possibly high-dimensional) conditional density of the mediators, instead allowing for regression methods, far more readily available throughout the statistics literature and software, to be used for estimation of the relevant quantities. Similar ideas have been used by Zheng and van der Laan [200], Díaz and Hejazi [35], and Daz et al. [42]. In addition to the expression for the efficient influence function in Lemma 5, it is important to understand the behavior of the difference $\mathsf{P}D_{\eta_1} - \theta$, which is expected to yield a second order term in differences $\eta_1 - \eta$, so that consistent estimation of θ is possible under consistent estimation of certain configurations of the parameters in η. As we will see in Theorems 4 and 5, this second-order term is fundamental in the construction of asymptotically linear estimators. Lemmas 8 and 9, found in the 4.8, delinate these second-order terms. The following lemma is a direct consequence.

Lemma 6 (Multiple robustness for modified treatment policies)**.** *Let the modified treatment policy satisfy A6, and let η_1 be such that one of the following conditions hold:*

	$\mathsf{m}_1 = \mathsf{m}$	$\mathsf{g}_1 = \mathsf{g}$	$\mathsf{b}_1 = \mathsf{b}$	$\bar{\mathsf{u}}_1 = \bar{\mathsf{u}}$	$\mathsf{v}_1 = \mathsf{v}$	$\mathsf{d}_1 = \mathsf{d}$	$\mathsf{e}_1 = \mathsf{e}$	$\mathsf{s}_1 = \mathsf{s}$	$\mathsf{q}_1 = \mathsf{q}$
Cond. 1	×	×	×						
Cond. 2	×	×			×			×	
Cond. 3		×	×			×	×		
Cond. 4		×		×	×	×	×		
Cond. 5	×		×	×					×
Cond. 6	×			×	×			×	×

Table 4.1: Different configurations of consistency for nuisance parameters.

Then $\mathsf{P}D^1_{\eta_1,\delta} = \theta_{1,\delta}$ and $\mathsf{P}D^2_{\eta_1,\delta} = \theta_{2,\delta}$, with $D^1_{\eta,\delta}$ and $D^2_{\eta,\delta}$ as defined in Theorem 3 and Lemma 3.

The above lemma implies that it is possible to construct consistent estimators for for the (in)direct effects under consistent estimation of subsets of the nuisance parameters in η, in the configurations described in the lemma. Lemma 6 follows directly from Lemma 8, found in the 4.8. Some readers may find it surprising that estimation of $\theta_{j,\delta}$ may be robust to inconsistent estimation of g, even when the parameter definitions are explicitly dependent on g. We offer some intuition into this result by noting that assumption A6 allows use of the change of variable formula to obtain

$$\theta_{2,\delta} = \mathbb{E}\left\{\int \mathsf{m}(z, l, d(A, W), W)\mathsf{p}(l \mid d(A, W), W)\mathsf{p}(z \mid W)\mathrm{d}\nu(z, l)\right\}.$$

Estimation of this parameter without relying on g may be carried out by consistently estimating $\mathsf{m}(z, l, a, w)$, $\mathsf{p}(l \mid a, w)$, and $\mathsf{p}(z \mid w)$ and using the empirical distribution as an estimator of the outer expectation. This behavior has been previously observed for related stochastic intervention effects under assumption A6 [37, 68, 35].

The robustness result for the case an exponentially tilted intervention (4.1), which does not satisfy assumption A6, is presented in the following lemma

Lemma 7 (Multiple robustness for exponential tilting)**.** *Let g_δ be defined as in (4.4). Let η_1 be such that at least one of Cond. 1-4 in Table 4.1 holds. Then $\mathsf{P}D^1_{\eta_1,\delta} = \theta_{1,\delta}$ and $\mathsf{P}D^2_{\eta_1,\delta} = \theta_{2,\delta}$, with $D^1_{\eta,\delta}$ and $D^2_{\eta,\delta}$ as defined in Theorem 3 and Lemma 4*

Lemma 7 is a direct consequence of Lemma 9 in the 4.8. The corresponding proof reveals that the EIF for the binary distribution is not robust to inconsistent estimation of g — that is, the intervention fails to satisfy assumption A6 and integrals over the range of A cannot be computed using

the change of variable formula. This behavior has been previously observed for other interventions that do not satisfy assumption A6 [e.g., 36]. Even though this lemma implies that consistent estimation of g is required, the bias terms remain second-order; thus, an estimator of g converging at rate $n^{1/4}$ or faster is sufficient.

4.4 Efficient Estimation and Statistical Inference

We discuss two efficient estimators that rely on the efficient influence function $D_{\eta,\delta}$, in order to build an estimator that is both efficient and robust to model misspecification. We discuss an asymptotic linearity result for the doubly robust estimator that allows computation of asymptotically correct confidence intervals and hypothesis tests. In the sequel, we assume that preliminary estimators of the components of η are available. These estimators may be obtained from flexible regression techniques such as support vector machines, regression trees, boosting, neural networks, splines, or ensembles thereof [193, 17, 176]. As previously discussed, the consistency of these estimators determines consistency of our estimators of $\theta_{j,\delta}$.

Both of our proposed efficient estimators make use of the EIF $D_{\eta,\delta}$ to revise an initial substitution estimator through a bias correction step. As such, estimation proceeds by first constructing initial estimators of the nuisance parameters in η; then, each of the efficient estimators is constructed by application of distinct bias-correction steps. In constructing the these efficient estimators, we advocate for the use of cross-fitting [94, 199, 25] to avoid imposing entropy conditions on the initial estimators of the nuisance parameters in η. Let $\mathcal{V}_1, \ldots, \mathcal{V}_J$ denote a random partition of the index set $\{1, \ldots, n\}$ into J prediction sets of approximately the same size. That is, $\mathcal{V}_j \subset \{1, \ldots, n\}$; $\bigcup_{j=1}^{J} \mathcal{V}_j = \{1, \ldots, n\}$; and $\mathcal{V}_j \cap \mathcal{V}_{j'} = \emptyset$. For each j, the associated training sample is given by $\mathcal{T}_j = \{1, \ldots, n\} \setminus \mathcal{V}_j$, and we let $j(i)$ denote the index of the validation set which contains observation i. Denote by $\hat{\eta}_j$ the estimator of η obtained by training a prediction algorithm using only data in the sample $\mathcal{T}_j$.

Efficient One-Step Estimator

To construct a robust and efficient estimator using the efficient influence function $D_{\eta,\delta}$, the one-step bias correction [127, 14] adds the empirical mean of the estimated EIF $D_{\hat{\eta},\delta}$ to an initial substitution estimator. The estimators are thus defined

$$\begin{aligned} \hat{\psi}^{\text{os}}_{\text{D},\delta} &= \frac{1}{n} \sum_{i=1}^{n} \{D^1_{\hat{\eta}_{j(i)},0}(O_i) - D^2_{\hat{\eta}_{j(i)},\delta}(O_i)\} \\ \hat{\psi}^{\text{os}}_{\text{I},\delta} &= \frac{1}{n} \sum_{i=1}^{n} \{D^2_{\hat{\eta}_{j(i)},\delta}(O_i) - D^1_{\hat{\eta}_{j(i)},\delta}(O_i)\}. \end{aligned} \tag{4.17}$$

Asymptotic linearity and efficiency of estimators for modified treatment policies follows.

Theorem 4 (Weak convergence of one-step estimators)**.** *Let* $\|\cdot\|$ *denote the* $L_2(\mathsf{P})$*-norm defined as* $\|f\|^2 = \int f^2 \mathrm{d}\mathsf{P}$*. Define the following assumptions.*

(i) $\mathsf{P}\{|D^j_{\eta,\delta}(O)| \leq C\} = \mathsf{P}\{|D^j_{\hat{\eta},\delta}(O)| \leq C\} = 1$ *for* $j = 1, 2$ *and for some* $C < \infty$*.*

(ii) The following second-order terms converge at the specified rate

- $\|\hat{\mathsf{m}} - \mathsf{m}\| \left\{\|\hat{\mathsf{g}} - \mathsf{g}\| + \|\hat{\mathsf{e}} - \mathsf{e}\| + \left\|\hat{\mathsf{d}} - \mathsf{d}\right\|\right\} = o_{\mathsf{P}}(n^{-1/2})$
- $\|\hat{\mathsf{g}} - \mathsf{g}\| \left\{\left\|\hat{\bar{\mathsf{u}}} - \bar{\mathsf{u}}\right\| + \|\hat{\mathsf{q}} - \mathsf{q}\|\right\} = o_{\mathsf{P}}(n^{-1/2})$
- $\left\|\hat{\mathsf{b}} - \mathsf{b}\right\| \left\{\|\hat{\mathsf{v}} - \mathsf{v}\| + \|\hat{\mathsf{s}} - \mathsf{s}\|\right\} = o_{\mathsf{P}}(n^{-1/2})$*, and*

(iii) The effect is defined in terms of modified treatment policy $d(a, w)$*, which is piecewise smooth invertible (A6).*

(iv) The intervention g_δ *is an exponential tilting intervention and* $\mathsf{P}\left\{\int(\hat{\mathsf{g}} - \mathsf{g})\mathrm{d}\kappa\right\}^2 = o_{\mathsf{P}}(n^{-1/2})$*.*

If assumptions (i) and (ii) hold, and one of assumptions (iii) and (iv) holds, then:

$$\sqrt{n}\{\hat{\psi}^{os}_{D,\delta} - \psi_{D,\delta}\} \rightsquigarrow N(0, \sigma^2_{D,\delta}), \text{ and}$$
$$\sqrt{n}\{\hat{\psi}^{os}_{I,\delta} - \psi_{I,\delta}\} \rightsquigarrow N(0, \sigma^2_{I,\delta}),$$

where $\sigma^2_{D,\delta} = \mathrm{Var}\{D^1_{\eta,0}(O) - D^2_{\eta,\delta}(O)\}$ *and* $\sigma^2_{I,\delta} = \mathrm{Var}\{D^2_{\eta,\delta}(O) - D^1_{\eta,\delta}(O)\}$ *are the respective efficiency bounds.*

Theorem 4 establishes the weak convergence of $\hat{\psi}^{\mathrm{os}}_{\mathrm{D},\delta}$ and $\hat{\psi}^{\mathrm{os}}_{\mathrm{I},\delta}$ pointwise in δ. This convergence is useful to derive confidence intervals in situations where the modified treatment policy has a suitable scientific interpretation for a given realization of δ. Under Theorem 4, an estimator $\hat{\sigma}^2_{\mathrm{D},\delta}$ of $\sigma^2_{\mathrm{D},\delta}$ may be obtained as the empirical variance of $D^1_{\hat{\eta}_{j(i)},0}(O_i) - D^2_{\hat{\eta}_{j(i)},\delta}(O_i)$, and a Wald-type confidence interval may be constructed as $\hat{\psi}^{\mathrm{os}}_{\mathrm{D},\delta} \pm z_{1-\alpha/2}\hat{\sigma}^2_{\mathrm{D}}(\delta)/\sqrt{n}$; the same applies to $\hat{\psi}^{\mathrm{os}}_{\mathrm{I},\delta}$.

Although the one-step estimator has optimal asymptotic performance, its finite-sample behavior may be affected by the inverse probability weighting involved in the computation of the efficient influence functions $D^j_{\hat{\eta}}(O_i) : j = 1, 2$. In particular, it is not guaranteed that $\hat{\psi}^{\mathrm{os}}_{\mathrm{D},\delta}$ and $\hat{\psi}^{\mathrm{os}}_{\mathrm{I},\delta}$ will remain within the bounds of the parameter space. This issue may be attenuated by performing weight stabilization. The estimated EIF $D^1_{\hat{\eta}_{j(i)}}(O_i)$ can be weight-stabilized by dividing (4.9) and (4.11) by the empirical mean of $H^1_{\hat{\eta}_j(i),\delta}(A_i, Z_i, L_i, W_i)$ and $H^2_{\hat{\eta}_j(i),\delta}(A_i, Z_i, L_i, W_i)$, respectively; as well as dividing (4.10), (4.12), (4.13), and (4.14) by the empirical mean of $\hat{\mathsf{g}}_{j(i),\delta}(A_i \mid W_i)/\hat{\mathsf{g}}_{j(i)}(A_i \mid W_i)$.

Efficient Targeted Minimum Loss Estimator

Although corrections may be applied to the one-step estimator, a more principled way to obtain estimators that remain in the parameter space may be derived from the targeted minimum loss (TML) estimation framework. The TML estimator is constructed by tilting an initial data adaptive estimator $\hat{\eta}$ towards a solution $\tilde{\eta}$ of the estimating equations

$$\begin{aligned} \mathsf{P}_n\{D^1_{\tilde{\eta},0} - D^2_{\tilde{\eta},\delta}\} &= \psi_{\mathrm{D},\delta}(\tilde{\eta}) \\ \mathsf{P}_n\{D^2_{\tilde{\eta},\delta} - D^1_{\tilde{\eta},\delta}\} &= \psi_{\mathrm{I},\delta}(\tilde{\eta}), \end{aligned} \tag{4.18}$$

where $\psi_{\mathrm{D},\delta}(\tilde{\eta})$ and $\psi_{\mathrm{I},\delta}(\tilde{\eta})$ are the substitution estimators in formula (4.19) obtained by plugging in the estimates $\tilde{\eta}$ in the parameter definition (4.6). Thus, a TML estimator is guaranteed to remain in the parameter space by virtue of its being a substitution estimator. The fact that the nuisance estimators solve the relevant estimating equation is used to obtain a weak convergence result analogous to Theorem 4. Thus, while the TML estimator is expected to attain the same optimal asymptotic behavior as the one-step estimator, its finite-sample behavior may be better. An algorithm to compute a TML estimator $\tilde{\eta}$ is presented in the 4.8. Roughly, the algorithm proceeds by projecting the EIF into score functions for the model of each nuisance parameter, and fitting appropriate parametric submodels [179, 178]. For example, the following model is fitted for m:

$$\operatorname{logit} \mathsf{m}_\beta(a,z,l,w) = \operatorname{logit} \hat{\mathsf{m}}(z,l,a,w) + \beta_I H_{\mathrm{I}}(o) + \beta_D H_{\mathrm{D}}(o), \quad \text{where}$$

$$\begin{aligned} H_{\mathrm{D}}(o) &= \frac{\hat{\mathsf{b}}(l \mid a,w)}{\hat{\mathsf{d}}(l \mid z,a,w)} \left\{ 1 - \frac{\hat{\mathsf{g}}_\delta(a \mid w)}{\hat{\mathsf{e}}(a \mid z,w)} \right\} \\ H_{\mathrm{I}}(o) &= \frac{\hat{\mathsf{b}}(l \mid a,w)}{\hat{\mathsf{d}}(l \mid z,a,w)} \left\{ \frac{\hat{\mathsf{g}}_\delta(a \mid w)}{\hat{\mathsf{e}}(a \mid z,w)} - \frac{\hat{\mathsf{g}}_\delta(a \mid w)}{\hat{\mathsf{g}}(a \mid w)} \right\}, \end{aligned}$$

and $\operatorname{logit}(p) = \log\{p(1-p)^{-1}\}$. Here, the initial estimator $\operatorname{logit} \hat{\mathsf{m}}(z,l,a,w)$ is considered a fixed offset variable (i.e., a variable with known parameter value equal to one). The score of these tilting models is equal to the corresponding component of the efficient influence function. The parameter $\beta = (\beta_I, \beta_D)$ may be estimated by running standard logistic regression of Y on $(H_{\mathrm{D}}(O), H_{\mathrm{I}}(O))$ with no intercept and an offset term equal to $\operatorname{logit} \hat{\mathsf{m}}(z,l,a,w)$. Let $\hat{\beta}$ denote the MLE, and let $\tilde{\mathsf{m}} = \mathsf{m}_{\hat{\beta}}$ denote the updated estimates. Fitting this model ensures that $\tilde{\mathsf{m}}$ solves the relevant score equations. Models like this are estimated iteratively for all parameters in a way that guarantees that the estimating equations (4.18) are solved up to a term that converges to zero in probability at rate

faster than $n^{-1/2}$. After the iteration ends, the TML estimators are defined as

$$\begin{aligned}\hat{\psi}^{\text{tmle}}_{\text{D},\delta} &= \frac{1}{n}\int \sum_{i=1}^{n} \left\{\tilde{\bar{\mathfrak{u}}}(a, W_i)\tilde{\mathfrak{g}}(a \mid W_i) - \tilde{\mathfrak{u}}(Z_i, a, W_i)\tilde{\mathfrak{g}}_\delta(a \mid W_i)\right\} \mathrm{d}\kappa(a) \\ \hat{\psi}^{\text{tmle}}_{\text{I},\delta} &= \frac{1}{n}\int \sum_{i=1}^{n} \left\{\tilde{\mathfrak{u}}(Z_i, a, W_i) - \tilde{\bar{\mathfrak{u}}}(a, W_i)\right\} \tilde{\mathfrak{g}}_\delta(a \mid W_i) \mathrm{d}\kappa(a).\end{aligned} \tag{4.19}$$

The fact that the TML estimator solves estimating equations (4.18) is a fundamental step in proving the following theorem.

Theorem 5 (Weak convergence of TML estimator)**.** *Assume (i) and (ii) hold, and one of (iii), (iv) defined in Theorem 4 holds, then:*

$$\begin{aligned}\sqrt{n}\{\hat{\psi}^{tmle}_{D,\delta} - \psi_{D,\delta}\} &\rightsquigarrow N(0, \sigma^2_{D,\delta}), \text{ and} \\ \sqrt{n}\{\hat{\psi}^{tmle}_{I,\delta} - \psi_{I,\delta}\} &\rightsquigarrow N(0, \sigma^2_{I,\delta}),\end{aligned}$$

where $\sigma^2_{D,\delta} = \mathrm{Var}\{D^1_{\eta,0}(O) - D^2_{\eta,\delta}(O)\}$ *and* $\sigma^2_{I,\delta} = \mathrm{Var}\{D^2_{\eta,\delta}(O) - D^1_{\eta,\delta}(O)\}$.

Using Theorem 5, asymptotically valid variance estimators, p-values, and confidence intervals for the (in)direct effects may be obtained in a manner analogous to those for the one-step estimator. The proof of the theorem proceeds using similar arguments as the proof of Theorem 4 for the one-step estimator, using empirical process theory and leveraging cross-fitting to avoid entropy conditions on the initial estimators of η. Since the estimators now depend on the full sample through the estimates of the parameters β of the logistic tilting models, the empirical process treatment differs slightly to that of Theorem 4; its proof is detailed in the 4.8.

4.5 Simulation Study

We used simulation experiments to assess our two proposed efficient estimators of the (in)direct effects. On account of computational considerations, we focus on binary exposures and intermediate confounders in this example; however, as noted in the prior, our proposed methodology is general enough to be readily applicable in the presence of continuous-valued covariates, treatment, mediators, intermediate confounders, and outcome. We used the following data-generating mechanism

for the joint distribution of O to generate synthetic data for evaluation of the two estimators:

$$\begin{aligned}
W_1 &\sim \text{Bernoulli}(p = 0.6); W_2 \sim \text{Bernoulli}(p = 0.3); \\
W_3 \mid (W_1, W_2) &\sim \text{Bernoulli}(p = 0.2 + 1/3 \cdot (W_1 + W_2)); \\
A \mid W &\sim \text{Bernoulli}(p = \text{expit}(2 + (5/(W_1 + W_2 + W_3)))); \\
L \mid (A, W) &\sim \text{Bernoulli}(p = \text{expit}(1/3(W_1 + W_2 + W_3) - A - \log(2) + 0.2)); \\
Z \mid (L, A, W) &\sim \text{Bernoulli}(p = \text{expit}(\log(3) \cdot (W_1 + W_2) + A - L)); \\
Y \mid (Z, L, A, W) &\sim \text{Bernoulli}\left(p = \text{expit}\left(1 - \frac{3 \cdot (3 - L - 3A + Z)}{2 + (W_1 + W_2 + W_3)}\right)\right),
\end{aligned}$$

where $\text{expit}(x) := \{1 + \exp(x)\}^{-1}$. For each of the sample sizes $n \in \{200, 800, 1800, 3200, 5000, 7200, 9800, 12800, 16200\}$, 500 datasets were generated. For every dataset, six variations of each of the two efficient estimators was applied — five variants were based on misspecification of a single nuisance parameter among $\{\mathsf{e}, \mathsf{m}, \mathsf{d}, \mathsf{g}, \mathsf{b}\}$ while the sixth variant was constructed based on consistent estimation of all five nuisance parameters. An intercept-only logistic regression model provided inconsistent estimation of each of the nuisance parameters $\{\mathsf{e}, \mathsf{m}, \mathsf{d}, \mathsf{g}, \mathsf{b}\}$, while a Super Learner ensemble [176] was used to achieve consistent estimation. The Super Learner ensemble was constructed with a library of algorithms composed of intercept-only logistic regression; main-terms logistic regression; and several variants of the highly adaptive lasso [11, 167, 75, 30], a nonparametric regression approach capable of flexibly estimating arbitrary functional forms at a fast convergence rate under only a global smoothness assumption [170, 13]. Note that we do not consider cases of misspecified estimation of $\{\mathsf{v}, \mathsf{s}, \mathsf{q}, \bar{\mathsf{u}}\}$, as their consistent estimation depends on a subset of the nuisance parameters $\{\mathsf{e}, \mathsf{m}, \mathsf{d}, \mathsf{g}, \mathsf{b}\}$. Generally, based on Lemmas 6 and 7, robustness of the direct and indirect effect estimators to misspecification of $\{\mathsf{e}, \mathsf{m}, \mathsf{d}\}$ is to be expected, but the same is not true under misspecification of $\{\mathsf{g}, \mathsf{b}\}$.

Figure 16 summarizes the results of our investigations of the relative performance of the estimator variants enumerated above. Specifically, we assess the relative performance of our proposed estimators in terms of absolute bias, scaled (by $n^{1/2}$) bias, standard error and scaled (by n) mean squared error relative to the efficiency bound for the data-generating model, the empirical coverage of 95% confidence intervals, and relative efficiency. In terms of both raw (unscaled) bias and scaled bias, the estimator variants appear to conform to the predictions of Lemmas 6 and 7 — specifically, raw bias vanishes and scaled bias stabilizes to a small value (providing evidence for rate-consistency) under misspecification of any of $\{\mathsf{e}, \mathsf{m}, \mathsf{d}\}$ as well as in the case of no nuisance parameter misspecification. In the same vein, when either of $\{\mathsf{g}, \mathsf{b}\}$ are estimated inconsistently, some of the estimator variants display diverging asymptotic (scaled) bias, in agreement with expectations based upon theory. The consistency of other estimator variants (e.g., the one-step estimator

under misspecification of b) is likely an artifact of this data-generating mechanism, not to be taken as a general indication of robust performance. In terms of their relative mean squared error, the estimators of the (in)direct effects exhibit convergence to the efficiency bound under misspecification of $\{\mathsf{e}, \mathsf{m}, \mathsf{d}\}$ and under no misspecification; this also appears to hold for a subset of the estimator variants under misspecification of $\{\mathsf{g}, \mathsf{b}\}$. We stress that aspects of this are likely to be a particularity of the given data-generating mechanism or on account of the irregularity of misspecified estimator variants, for the regularity and asymptotically linearity of the estimators is only to be expected under consistent estimation of all nuisance parameters. Finally, the empirical coverage of 95% confidence intervals is as expected: under a lack of nuisance parameter misspecification, both the one-step and TML estimators of the direct and indirect effect achieve 95% coverage in larger sample sizes. We note that misspecification of e leads to over-coverage for all estimator variants, implying an overly inflated variance estimate, while the confidence intervals fail to attain the nominal rate in most other instances. Notably, several of the estimator variants generate confidence intervals that are liable to converge to 0% coverage in larger samples under misspecification of $\{\mathsf{g}, \mathsf{b}\}$, very much in line with theoretical expectations.

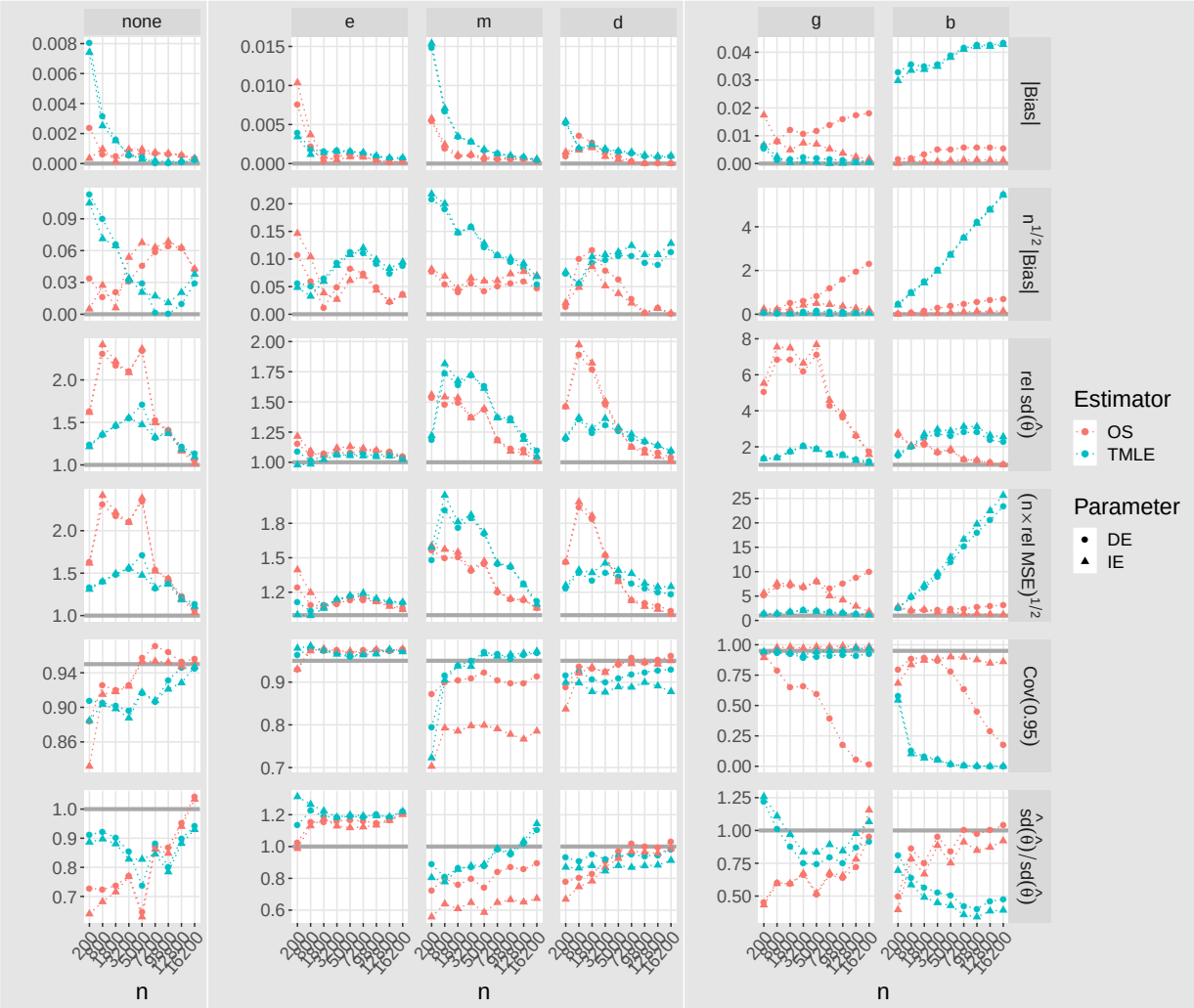

Figure 16: Comparison of efficient estimators across different nuisance parameter configurations.

Importantly, the TML estimator appears to generally outperform the one-step estimator throughout several scenarios. This comes in several forms, including lower bias, relative standard deviation, or relative mean squared error under misspecification of $\{\mathsf{e}, \mathsf{m}, \mathsf{d}\}$ or under no misspecification; however, under inconsistent estimation of $\{\mathsf{g}, \mathsf{b}\}$, the irregularity of the estimators complicates this comparison. Interestingly, under misspecification of g, the TML estimators of the direct and indirect effects appear unbiased and efficient, a result unpredictable from theory given the irregularity of the estimators under this configuration. Altogether, results of our numerical experiments indicate that our proposed estimators exhibit properties that align with the theoretical results of Lemmas 6 and 7.

4.6 Application to the X:BOT Trial

We now consider the application of our proposed stochastic interventional direct and indirect effects to decompose the causal effect of a strategy where buprenorphine dose is successively increased early in treatment (regardless of opioid use) on relapse among those with opioid use disorder (OUD). Data for our illustrative analysis come from the X:BOT trial, a 24-week, multi-site randomized controlled trial designed to examine the comparative effectiveness of extended-release naltrexone (XR-NTX) and sublingual buprenorphine-naloxone (BUP-NX) on relapse [98, 99, 114]. The X:BOT trial enrolled 570 participants, all of whom were 18 years or older, had OUD [as per the Diagnostic and Statistical Manual of Mental Disorders-5; 1], and had used non-prescribed opioids in the 30 days preceding enrollment. Participants were randomized to receive either XR-NTX or BUP-NX using a stratified permuted block design; 287 of the 570 were randomized to receive BUP-NX. Prior analytic efforts have established a protective effect of BUP-NX administration (versus placebo) on OUD relapse [106]. For each participant assigned to receive BUP-NX, the prescribed dose was based on both clinical indication [98] and clinician judgment. Some clinicians tended to hold dose constant over time (i.e., a static regimen), while others increased dose — either based on clinical assessment or on the hypothesis that higher doses would result in better outcomes [115, 65, 28, 71]. In this analysis, we estimated hypothetical stochastic interventional (in)direct effects to assess the mechanism by which universally ramping up BUP-NX dose early in treatment (defined as three or more dose increases in the first four weeks of treatment) could mitigate the risk of OUD relapse.

Baseline covariates (W) available in the data included site; gender; age; race/ethnicity; homeless status; educational attainment; employment status; marital status; current intravenous drug use; alcohol use disorder; cocaine use disorder; age at start of heroin use; severity of current opioid use; indicator of prior OUD treatment; past withdrawal discomfort level; histories of amphetamine use, sedative use, and cannabis use; weekly cost of primary drug; whether or not living with an individual currently using drugs or with alcohol use disorder; histories of psychiatric illnesses; randomization timing; baseline pain level; baseline depression symptoms. The exposure (A) was taken to be successive increases in dose of BUP-NX versus static dose, measured during the first four weeks of treatment. Mediating factors (Z) included depression and pain, measured from week 6 until relapse or week 24 (end of follow-up). Abstinence from illicit opioid use early in the treatment schedule, measured between weeks 4 and 6, acted as an intermediate confounder affected by exposure (L). OUD relapse status at the X:BOT trial's end of follow-up was the outcome of interest (Y). To examine the effect of exposure to successive increases in BUP-NX dose, we consider an incremental propensity score intervention, which, for binary A, replaces the propensity score $g(1 \mid w)$ with a shifted variant constructed from multiplying the odds of treatment by a user-

specified parameter δ [91], which we vary along a grid $\log(\delta) \in \{-10.0, -9.5, \ldots, 9.5, 10.0\}$ of the exposure odds observed in the X:BOT trial. Across all such estimates in the odds δ of exposure, the stochastic interventional (in)direct effects that we estimated may be interpreted in terms of the overall effect of increasingly encouraging ramping up BUP-NX dose early in treatment on the counterfactual risk of OUD relapse; thus, the results of our analysis may be informative of the mechanisms by which increasing BUP-NX dose can alter the risk of OUD relapse. Figure 17 presents the direct and indirect effect estimates across the grid in δ.

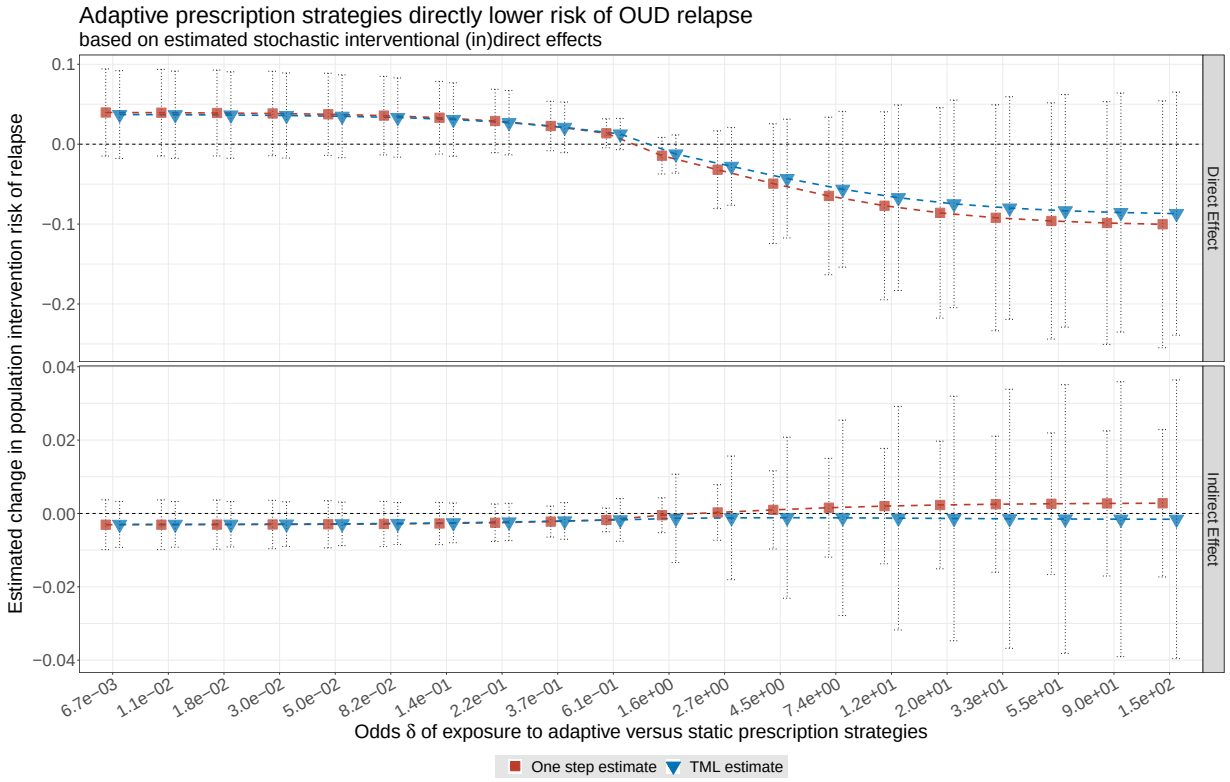

Figure 17: Stochastic interventional direct (upper panel) and indirect (lower panel) effect estimates of a hypothetical intervention increasing odds of exposure to a BUP-NX dose schedule in which dose is successively increased early in OUD relapse treatment across a grid of shifts δ in the odds.

We applied both of our cross-fitted, efficient one-step and TML estimators to examine the stochastic interventional direct and indirect effects of increasing the odds of ramping up BUP-NX dose. Both estimation strategies produced results that were generally in very close agreement as to the magnitude of the direct and indirect effects. For each point estimate, standard error estimates and 95% Wald-style confidence intervals were constructed based on the conclusions of Theorem 5. In order to ensure the flexibility of our estimators, each component of the vector

of nuisance parameters $\eta = (\mathsf{e}, \mathsf{m}, \mathsf{d}, \mathsf{g}, \mathsf{b})$ was estimated via ensemble machine learning, using the Super Learner algorithm [176, 31]. The library of machine learning algorithms from which the Super Learner ensemble was constructed included intercept-only logistic regression, logistic regression with Bayesian priors on parameters, multivariate adaptive regression splines [55], generalized additive models [69], random forests [16], gradient boosted machines [54], and the highly adaptive lasso [11, 30, 75].

From examination of the point estimates and confidence intervals of the direct and indirect effects in Figure 17, two conclusions may be drawn. Firstly, there appears to be little to no indirect effect of successively increasing BUP-NX dose on risk of OUD relapse, revealing that any effect of BUP-NX dose does not appear to operate through mediating factors such as depression or pain. Secondly, the direct effect of successively increasing BUP-NX dose varies considerably across changes in the odds of the introduction of such a dose schedule. Importantly, it appears that decreasing the odds of increasing dose could lead to as much as a 5% increase in the OUD relapse risk, with a plateau emerging at odds lower than $\approx$0.1%, suggesting that static dose can lead to increased relapse risk relative to successive dose increases. Continuing this pattern, OUD relapse risk appears to decrease by $\approx$10% with increasing odds of successively increasing BUP-NX dose, with the risk plateauing at odds higher than 33%. This decrease in the counterfactual risk of OUD relapse suggests a protective effect of BUP-NX dose schedules where dose is successively increased early in treatment relative to static dose.

The conclusions that may be drawn from our re-analysis using the stochastic interventional direct and indirect effects complement those previously reported in the investigations of Lee et al. [98], who evaluated the total effect of BUP-NX (versus XR-NTX) treatment on OUD relapse, and Rudolph et al. [151], who used the interventional mediation analysis approach of Daz et al. [42] (limited to static interventions on A) to examine differences in relapse risk between homeless and non-homeless participants. Importantly, our substantive conclusion — that dose increases directly lower the risk of relapse — agree generally with those of Rudolph et al. [150], who found that dose increases directly lowered risk of OUD relapse when such dose increases followed opioid use. Notably, our proposed (in)direct effects and estimation approach differ from previous efforts in three important ways: (i) our causal effect definitions remain unaltered in the presence intermediate confounders affected by exposure and may be re-evaluated in randomized trials, (ii) the flexible estimators we introduce eschew restrictive modeling assumptions by incorporating state-of-the-art machine learning in the estimation of nuisance parameters, and (iii) our strategy provides an analog to a dose-response analysis by allowing for the risk of OUD relapse to be traced out across changes in the odds of exposure to a schedule in which BUP-NX dose is increased repeatedly early in treatment.

4.7 Discussion

We have proposed a class of novel direct and indirect effects for causal mediation analysis, as well as two efficient estimators of these effects in the nonparametric statistical model. Importantly, our proposed estimation framework allows for data adaptive estimation of nuisance parameters, while still preserving the benefits associated with similar classical techniques — that is, our estimators are regular and asymptotically linear, provide unbiased point estimates, are multiply robust, allow the construction of asymptotically valid confidence intervals, and are capable of attaining the nonparametric efficiency bound. Our (in)direct effects have interpretations that echo those of the classical natural (in)direct effects; however, our effects remain well-defined even in the presence of intermediate confounders affected by exposure. Further, any scientific conclusions drawn based upon our proposed (in)direct effects may be readily interrogated in trials that randomize both the exposure and mediators. Such flexible effect definitions and estimators seem necessary both to cope with the design complexity exhibited by modern epidemiological and biomedical studies and to take appropriate advantage of the ever-growing number of data adaptive regression techniques.

The challenge of leveraging data adaptive regression methodology to construct robust estimators that accommodate valid statistical inference is not a new one. It has been considered in great detail as early as the work of Pfanzagl and Wefelmeyer [127] as well in numerous recent advances, most notably by van der Laan and Rose [179, 178] and Chernozhukov et al. [25]; related work by these authors presents a wealth of extensions and applications. In the present work, we derive multiply robust, efficient estimators based on both the one-step and targeted minimum loss estimation frameworks. Following Klaassen [94] and Zheng and van der Laan [199], our estimators leverage cross-validation to avoid imposing possibly restrictive assumptions on nuisance function estimators. We demonstrated the properties of our estimators in simulation experiments that illustrated their ability to yield unbiased point estimates, attain the nonparametric efficiency bound, and build confidence intervals covering at the nominal rate across several nuisance parameter configurations — all within a problem context in which classical mediation effects are ill-defined. We demonstrated the application of our novel (in)direct effects in dissecting the mechanism by which increasing odds of adopting a dose schedule of universal successive increases in buprenorphine dose early in treatment affects OUD relapse [98, 151].

Several significant extensions and refinements are left for future consideration. Firstly, our proposed estimation strategy for the direct and indirect effects leverages re-parameterizations of factors of the likelihood in order to simplify the estimation of nuisance parameters. This approach works particularly well when either mediators or intermediate confounders are of low dimension; however, improving this approach to accommodate moderate dimensionality of both mediators and intermediate confounders would surely widen the range of scenarios to which the methodology

may be applied. Secondly, when defining effects based upon stochastic interventions indexed by the user-specified parameter δ, an important consideration is choosing *a priori* a particular value of δ. One solution is to evaluate a set of causal effects indexed by a grid in δ. In such cases, aggregate effects (across δ) may be summarized via working marginal structural models [e.g., 78] or the construction of uniform tests of the null hypothesis of no direct effect [e.g., 35]. Developments of these distinct summarization strategies would enrich the range of scientific problems on which these robust and flexible (in)direct effects may be brought to bear.

4.8 Supplementary Material

Theorem 2

Proof First, we have

$$
\begin{aligned}
&\mathbb{E}\{Y_{A_\delta, G_\delta}\} \\
&= \int \mathbb{E}\left\{Y_{a,z} \mid A_\delta = a, G_\delta = z, W = w\right\} \mathsf{g}_\delta(a \mid w) \mathsf{P}(G_\delta = z \mid A_\delta = a, W = w) \mathsf{p}(w) \mathrm{d}\nu(a, z, w) \\
&= \int \mathbb{E}\left\{Y_{a,z} \mid W = w\right\} \mathsf{g}_\delta(a \mid w) \mathsf{P}(Z(a) = z \mid A_\delta = a, W = w) \mathsf{p}(w) \mathrm{d}\nu(a, z, w) \qquad (4.20) \\
&= \int \mathbb{E}\left\{Y_{a,z} \mid A = a, W = w\right\} \mathsf{g}_\delta(a \mid w) \mathsf{P}(Z(a) = z \mid W = w) \mathsf{p}(w) \mathrm{d}\nu(a, z, w) \qquad (4.21) \\
&= \int \mathbb{E}\left\{Y_{a,z} \mid A = a, W = w\right\} \mathsf{g}_\delta(a \mid w) \mathsf{P}(Z(a) = z \mid A = a, W = w) \mathsf{p}(w) \mathrm{d}\nu(a, z, w) \\
& \qquad (4.22) \\
&= \int \mathbb{E}\left\{Y_{a,z} \mid A = a, W = w, L = l\right\} \mathsf{b}(l \mid a, w) \mathsf{g}_\delta(a \mid w) \mathsf{p}(z \mid a, w) \mathsf{p}(w) \mathrm{d}\nu(a, z, l, w) \\
&= \int \mathsf{m}(a, z, l, w) \mathsf{b}(l \mid a, w) \mathsf{g}_\delta(a \mid w) \mathsf{p}(z \mid a, w) \mathsf{p}(w) \mathrm{d}\nu(a, z, l, w), \qquad (4.23)
\end{aligned}
$$

where (4.20) follows by definition of (A_δ, G_δ), (4.21) follows by A8 and definition of A_δ, (4.22) follows by A10, and (4.23) follows by A9. Similar arguments yield

$$
\mathbb{E}\{Y_{A,G}\} = \int \mathsf{m}(a, z, l, w) \mathsf{b}(l \mid a, w) \mathsf{g}(z \mid w) \mathsf{p}(z \mid a, w) \mathsf{p}(w) \mathrm{d}\nu(a, z, l, w).
$$

We also have

$$
\begin{aligned}
&\mathbb{E}\{Y_{A_\delta,G}\} \\
&= \int \mathbb{E}\left\{Y_{a,z} \mid A_\delta = a, G = z, W = w\right\} \mathsf{g}_\delta(a \mid w)\mathsf{P}(G = z \mid A_\delta = a, W = w)\mathsf{p}(w)\mathrm{d}\nu(a,z,w) \\
&= \int \mathbb{E}\left\{Y_{a,z} \mid W = w\right\} \mathsf{g}_\delta(a \mid w)\mathsf{P}(G = z \mid W = w)\mathsf{p}(w)\mathrm{d}\nu(a,z,w) \\
&= \int \mathbb{E}\left\{Y_{a,z} \mid A = a, W = w\right\} \mathsf{g}_\delta(a \mid w)\mathsf{p}(z \mid w)\mathsf{p}(w)\mathrm{d}\nu(a,z,w) \\
&= \int \mathbb{E}\left\{Y_{a,z} \mid A = a, W = w\right\} \mathsf{g}_\delta(a \mid w)\mathsf{p}(z \mid w)\mathsf{p}(w)\mathrm{d}\nu(a,z,w) \\
&= \int \mathbb{E}\left\{Y_{a,z} \mid A = a, W = w, L = l\right\} \mathsf{b}(l \mid a, w)\mathsf{g}_\delta(a \mid w)\mathsf{p}(z \mid w)\mathsf{p}(w)\mathrm{d}\nu(a,z,l,w) \\
&= \int \mathsf{m}(a,z,l,w)\mathsf{b}(l \mid a, w)\mathsf{g}_\delta(a \mid w)\mathsf{p}(z \mid w)\mathsf{p}(w)\mathrm{d}\nu(a,z,l,w).
\end{aligned}
$$

Subtracting gives the expressions for the PIIE and PIDE in the theorem. □

Efficient Influence Functions (Theorem 3)

Proof In this proof we will use $\Theta_j(\mathsf{P}) : j = 1, 2$ to denote a parameter as a functional that maps the distribution P in the model to a real number. We will assume that the measure ν is discrete so that integrals can be written as sums, and will omit the dependence on δ. It can be checked algebraically that the resulting influence function will also correspond to the influence function of a general measure ν. The true parameter value for θ_1 is thus given by

$$\theta_1 = \Theta_1(\mathsf{P}) = \sum_{y,a,z,m,w} y\, \mathsf{p}(y \mid a, z, l, w)\mathsf{p}(l \mid a, w)\mathsf{p}(z \mid a, w)\mathsf{g}_\delta(a \mid w)\mathsf{p}(w).$$

The non-parametric MLE of θ_1 in the model of g_δ known is given by

$$\Theta(\mathsf{P}_n) = \sum_{y,a,z,m,w} y \frac{\mathsf{P}_n f_{y,a,z,l,w}}{\mathsf{P}_n f_{a,z,l,w}} \frac{\mathsf{P}_n f_{l,a,w}}{\mathsf{P}_n f_{a,w}} \frac{\mathsf{P}_n f_{z,a,w}}{\mathsf{P}_n f_{a,w}} \mathsf{g}_\delta(a \mid w)\mathsf{P}_n f_w, \tag{4.24}$$

where we remind the reader of the notation $\mathsf{P}f = \int f \mathrm{d}\mathsf{P}$. Here $f_{y,a,z,l,w} = \mathbb{1}(Y = y, A = a, Z = z, M = m, W = w)$, and $\mathbb{1}(\cdot)$ denotes the indicator function. The other functions f are defined analogously.

We will use the fact that the efficient influence function in a non-parametric model corresponds with the influence curve of the NPMLE. This is true because the influence curve of any regular estimator is also a gradient, and a non-parametric model has only one gradient. The Delta method [see, e.g., Appendix 18 of 179] shows that if $\hat{\Theta}_1(\mathsf{P}_n)$ is a substitution estimator such that $\theta_1 =$

$\hat{\Theta}_1(\mathsf{P})$, and $\hat{\Theta}_1(\mathsf{P}_n)$ can be written as $\hat{\Theta}_1^*(\mathsf{P}_n f : f \in \mathcal{F})$ for some class of functions $\mathcal{F}$ and some mapping Θ_1^*, the influence function of $\hat{\Theta}_1(\mathsf{P}_n)$ is equal to

$$\mathrm{IF}_{\mathsf{P}}(O) = \sum_{f \in \mathcal{F}} \frac{\mathrm{d}\hat{\Theta}_1^*(\mathsf{P})}{\mathrm{d}\mathsf{P}f}\{f(O) - \mathsf{P}f\}.$$

Applying this result to (4.24) with $\mathcal{F} = \{f_{y,a,z,l,w}, f_{a,z,l,w}, f_{z,a,w}, f_{a',w}, f_{l,a,w}, f_{a,w}, f_w : y, a, z, l, w\}$ and rearranging terms gives the result of the theorem. The algebraic derivations involved here are lengthy and not particularly illuminating, and are therefore omitted from the proof. Similar analyses may be performed for the model where only g_δ is unknown, as well as θ_2. □

Targeted Minimum Loss Estimation Algorithm

To simplify notation, in the remaining of this section we will denote $\tilde{\eta}_{j(i)}(O_i)$ with $\tilde{\eta}(O_i)$. If L is binary, the efficient influence functions in Theorem 3 may be simplified using the following identity:

$$\mathsf{v}(l, a, w) - \bar{\mathsf{v}}(a, w) = \{\mathsf{v}(1, a, w) - \mathsf{v}(0, a, w)\}\{l - \mathsf{b}(1 \mid a, w)\},$$

which also holds for v replaced by s and $\bar{\mathsf{v}}$ by $\bar{\mathsf{s}}$.

Step 1. Initialize $\tilde{\eta} = \hat{\eta}$. Compute $\tilde{\mathsf{v}}$, $\tilde{\mathsf{s}}$, and $\tilde{\mathsf{q}}^j$ by plugging in $\tilde{\mathsf{m}}$, $\tilde{\mathsf{g}}$, $\tilde{\mathsf{e}}$, $\tilde{\mathsf{d}}$ into equations (4.7), (4.16) and (4.15) if Z is multivariate, and fitting data-adaptive regression algorithms as appropriate.

Step 2. For each subject, compute the auxiliary covariates

$$\begin{aligned}
H_{\mathrm{D},i} &= \frac{\tilde{\mathsf{b}}(L_i \mid A_i, W_i)}{\tilde{\mathsf{d}}(L_i \mid Z_i, A_i, W_i)} \left\{1 - \frac{\tilde{\mathsf{g}}_\delta(A_i \mid W_i)}{\tilde{\mathsf{e}}(A_i \mid Z_i, W_i)}\right\} \\
H_{\mathrm{I},i} &= \frac{\tilde{\mathsf{b}}(L_i \mid A_i, W_i)}{\tilde{\mathsf{d}}(L_i \mid Z_i, A_i, W_i)} \left\{\frac{\tilde{\mathsf{g}}_\delta(A_i \mid W_i)}{\tilde{\mathsf{e}}(A_i \mid Z_i, W_i)} - \frac{\tilde{\mathsf{g}}_\delta(A_i \mid W_i)}{\tilde{\mathsf{g}}(A_i \mid W_i)}\right\} \\
K_{\mathrm{D},i} &= \tilde{\mathsf{v}}(1, A_i, W_i) - \tilde{\mathsf{v}}(0, A_i, W_i) - \frac{\tilde{\mathsf{g}}_\delta(A_i \mid W_i)}{\tilde{\mathsf{g}}(A_i \mid W_i)}\{\tilde{\mathsf{s}}(1, A_i, W_i) - \tilde{\mathsf{s}}(0, A_i, W_i)\} \\
K_{\mathrm{I},i} &= \frac{\tilde{\mathsf{g}}_\delta(A_i \mid W_i)}{\tilde{\mathsf{g}}(A_i \mid W_i)}\{\tilde{\mathsf{s}}(1, A_i, W_i) - \tilde{\mathsf{s}}(0, A_i, W_i) - \tilde{\mathsf{v}}(1, A_i, W_i) + \tilde{\mathsf{v}}(0, A_i, W_i)\} \\
M_{\mathrm{D},i} &= -\frac{\tilde{\mathsf{g}}_\delta(1 \mid w)(1 - \tilde{\mathsf{g}}_\delta(1 \mid w))}{\tilde{\mathsf{g}}(1 \mid w)(1 - \tilde{\mathsf{g}}(1 \mid w))}\tilde{\mathsf{q}}^2(w) \\
M_{\mathrm{I},i} &= \frac{\tilde{\mathsf{g}}_\delta(1 \mid w)(1 - \tilde{\mathsf{g}}_\delta(1 \mid w))}{\tilde{\mathsf{g}}(1 \mid w)(1 - \tilde{\mathsf{g}}(1 \mid w))}\{\tilde{\mathsf{q}}^2(w) - \tilde{\mathsf{q}}^1(w)\}
\end{aligned}$$

Step 3. Fit the logistic tilting models

$$\begin{aligned}\operatorname{logit} \mathsf{m}_\beta(A_i, Z_i, L_i, W_i) &= \operatorname{logit} \tilde{\mathsf{m}}(A_i, Z_i, L_i, W_i) + \beta_I H_{\mathrm{I},i} + \beta_D H_{\mathrm{D},i} \\ \operatorname{logit} \mathsf{b}_\alpha(1 \mid A_i, W_i) &= \operatorname{logit} \tilde{\mathsf{b}}(1 \mid A_i, W_i) + \alpha_I K_{\mathrm{I},i} + \alpha_D K_{\mathrm{D},i} \\ \operatorname{logit} \mathsf{g}_\gamma(1 \mid W_i) &= \operatorname{logit} \tilde{\mathsf{g}}(1 \mid W_i) + \gamma_I M_{\mathrm{I},i} + \gamma_D M_{\mathrm{D},i}\end{aligned}$$

where $\operatorname{logit}(p) = \log\{p(1-p)^{-1}\}$. Here, $\operatorname{logit} \tilde{\mathsf{m}}(a, z, l, w)$ is an offset variable (i.e., a variable with known parameter value equal to one). The parameter $\beta = (\beta_I, \beta_D)$ may be estimated by running standard logistic regression of Y_i on $(H_{\mathrm{D},i}, H_{\mathrm{I},i})$ with no intercept and an offset term equal to $\operatorname{logit} \tilde{\mathsf{m}}(A_i, Z_i, L_i, W_i)$. Let $\hat{\beta}$ denote the estimate, and let $\tilde{\mathsf{m}} = \mathsf{m}_{\hat{\beta}}$ denote the updated estimates. Perform analogous computations for b and g.

Step 4. Compute $\tilde{\mathsf{u}}$ according to equation (4.7) by plugging in $\tilde{\mathsf{m}}$ and $\tilde{\mathsf{b}}$. Compute the covariate

$$J_i = \frac{\tilde{\mathsf{g}}_\delta(A_i \mid W_i)}{\tilde{\mathsf{g}}(A_i \mid W_i)},$$

and fit the model

$$\operatorname{logit} \bar{\mathsf{u}}_\kappa(A_i, W_i) = \operatorname{logit} \tilde{\bar{\mathsf{u}}}(A_i, W_i) + \kappa_D + \kappa_I J_i$$

by running a logistic regression of $\tilde{\mathsf{u}}(Z_i, A_i, W_i)$ on J_i with an intercept and offset $\operatorname{logit} \tilde{\bar{\mathsf{u}}}(A_i, W_i)$. Let $\hat{\kappa}$ denote the MLE, and update $\tilde{\bar{\mathsf{u}}} = \bar{\mathsf{u}}_{\hat{\kappa}}$.

Step 5. The TMLE of the direct and indirect effects are defined as:

$$\begin{aligned}\hat{\psi}^{\text{tmle}}_{\mathrm{D},\delta} &= \frac{1}{n} \int \sum_{i=1}^{n} \left\{ \tilde{\bar{\mathsf{u}}}(a, W_i) \tilde{\mathsf{g}}(a \mid W_i) - \tilde{\mathsf{u}}(Z_i, a, W_i) \tilde{\mathsf{g}}_\delta(a \mid W_i) \right\} \mathrm{d}\kappa(a) \\ \hat{\psi}^{\text{tmle}}_{\mathrm{I},\delta} &= \frac{1}{n} \int \sum_{i=1}^{n} \left\{ \tilde{\mathsf{u}}(Z_i, a, W_i) - \tilde{\bar{\mathsf{u}}}(a, W_i) \right\} \tilde{\mathsf{g}}_\delta(a \mid W_i) \mathrm{d}\kappa(a)\end{aligned}$$

Proof of Theorem 4

Proof Let $\mathsf{P}_{n,j}$ denote the empirical distribution of the prediction set $\mathcal{V}_j$, and let $\mathsf{G}_{n,j}$ denote the associated empirical process $\sqrt{n/J}(\mathsf{P}_{n,j} - \mathsf{P})$. For simplicity we denote a general parameter ψ with influence function D_η, the proof applies equally to the direct and indirect effect parameters. Note that

$$\hat{\psi}^{\text{os}}_\delta = \frac{1}{J} \sum_{j=1}^{J} \mathsf{P}_{n,j} D_{\hat{\eta}_j, \delta}, \quad \psi_\delta = \mathsf{P} D_\eta.$$

Thus,

$$\sqrt{n}\{\hat{\psi}^{\text{os}}_\delta - \psi_\delta\} = \mathsf{G}_n\{D_{\eta,\delta} - \psi_\delta\} + R_{n,1}(\delta) + R_{n,2}(\delta),$$

where

$$R_{n,1}(\delta) = \frac{1}{\sqrt{J}} \sum_{j=1}^{J} \mathsf{G}_{n,j}(D_{\hat{\eta}_j,\delta} - D_{\eta,\delta}), \quad R_{n,2}(\delta) = \frac{\sqrt{n}}{J} \sum_{j=1}^{J} \mathsf{P}\{D_{\hat{\eta}_j,\delta} - \psi_\delta\}.$$

It remains to show that $R_{n,1}(\delta)$ and $R_{n,2}(\delta)$ are $o_P(1)$. Lemmas 6 and 7 together with the Cauchy-Schwartz inequality and assumption (ii) of the theorem shows that $||R_{n,2}||_\Delta = o_P(1)$. For $||R_{n,1}||_\Delta$ we use empirical process theory to argue conditional on the training sample $\mathcal{T}_j$. In particular, Lemma 19.33 of [181] applied to the class of functions $\mathcal{F} = \{D_{\hat{\eta}_j,\delta} - D_{\eta,\delta}\}$ (which consists of one element) yields

$$E\left\{ \left| \mathsf{G}_{n,j}(D_{\hat{\eta}_j,\delta} - D_{\eta,\delta}) \right| \middle| \mathcal{T}_j \right\} \lesssim \frac{2C \log 2}{n^{1/2}} + ||D_{\hat{\eta}_j,\delta} - D_{\eta,\delta}||(\log 2)^{1/2}$$

By assumption (ii), the left hand side is $o_P(1)$. Lemma 6.1 of [25] may now be used to argue that conditional convergence implies unconditional convergence, concluding the proof. □

Theorem 5

Proof Let $\mathsf{P}_{n,j}$ denote the empirical distribution of the prediction set $\mathcal{V}_j$, and let $\mathsf{G}_{n,j}$ denote the associated empirical process $\sqrt{n/J}(\mathsf{P}_{n,j} - \mathsf{P})$. For simplicity we denote a general parameter ψ with influence function D_η, the proof applies equally to the direct and indirect effect parameters. By definition, the sum of the scores of the submodels $\{\mathsf{m}_\beta, \mathsf{b}_\alpha, \mathsf{g}_\gamma, \bar{\mathsf{u}}_\kappa : (\beta, \alpha, \gamma, \kappa)\}$ at the last iteration of the TMLE procedure is equal to $n^{-1} \sum_{i=1}^{n} D_{\tilde{\eta}}(O_i) = o_P(n^{-1/2})$. Thus, we have

$$\hat{\psi}_\delta^{\text{tmle}} = \frac{1}{J} \sum_{j=1}^{J} \mathsf{P}_{n,j} D_{\tilde{\eta}_j} + o_P(n^{-1/2}).$$

Thus,

$$\sqrt{n}(\hat{\psi}_\delta^{\text{tmle}} - \theta) = \mathsf{G}_n(D_\eta - \theta) + R_{n,1} + R_{n,2} + o_P(n^{-1/2}),$$

where

$$R_{n,1} = \frac{1}{\sqrt{J}} \sum_{j=1}^{J} \mathsf{G}_{n,j}(D_{\tilde{\eta}_j} - D_\eta), \quad R_{n,2} = \frac{\sqrt{n}}{J} \sum_{j=1}^{J} \mathsf{P}(D_{\tilde{\eta}_j} - \theta).$$

As in the proof of Theorem 4, Lemmas 6 and 7 together with the Cauchy-Schwartz inequality and the assumptions of the theorem shows that $R_{n,2} = o_P(1)$.

Since $D_{\tilde{\eta}_j}$ depends on the full sample through the estimates of the parameters β of the logistic tilting models, the empirical process treatment of $R_{n,1}$ needs to be slightly from that in the proof of Theorem 4. To make this dependence explicit, we introduce the notation $D_{\hat{\eta}_j,\beta} = D_{\tilde{\eta}_j}$ and $R_{n,1}(\beta)$.

Let $\mathcal{F}_n^j = \{D_{\hat{\eta}_j,\beta} - D_\eta : \beta \in B\}$. Because the function $\hat{\eta}_j$ is fixed given the training data, we can apply Theorem 2.14.2 of [184] to obtain

$$E\left\{\sup_{f\in\mathcal{F}_n^j} |\mathsf{G}_{n,j} f| \;\middle|\; \mathcal{T}_j\right\} \lesssim ||F_n^j|| \int_0^1 \sqrt{1 + N_{[]}(\epsilon||F_n^j||, \mathcal{F}_n^j, L_2(\mathsf{P}))}\mathrm{d}\epsilon,$$

where $N_{[]}(\epsilon||F_n^j||, \mathcal{F}_n^j, L_2(\mathsf{P}))$ is the bracketing number and we take $F_n^j = \sup_{\beta\in B} |D_{\hat{\eta}_j,\beta} - D_\eta|$ as an envelope for the class $\mathcal{F}_n^j$. Theorem 2.7.2 of [184] shows

$$\log N_{[]}(\epsilon||F_n^j||, \mathcal{F}_n^j, L_2(\mathsf{P})) \lesssim \frac{1}{\epsilon||F_n^j||}.$$

This shows

$$\begin{aligned}
||F_n^j|| \int_0^1 \sqrt{1 + N_{[]}(\epsilon||F_n^j||, \mathcal{F}_n^j, L_2(\mathsf{P}))}\mathrm{d}\epsilon &\lesssim \int_0^1 \sqrt{||F_n^j||^2 + \frac{||F_n^j||}{\epsilon}}\mathrm{d}\epsilon \\
&\leq ||F_n^j|| + ||F_n^j||^{1/2} \int_0^1 \frac{1}{\epsilon^{1/2}}\mathrm{d}\epsilon \\
&\leq ||F_n^j|| + 2||F_n^j||^{1/2}.
\end{aligned}$$

Since $||F_n^j|| = o_P(1)$, this shows $\sup_{f\in\mathcal{F}_n^j} \mathsf{G}_{n,j} f = o_P(1)$ for each j, conditional on $\mathcal{T}_j$. Thus $\sup_{\beta\in B} R_{n,1}(\beta) = o_P(1)$. Lemmas 6 and 7 together with the Cauchy-Schwartz inequality and the assumptions of the theorem show that $R_{n,2} = o_P(1)$, concluding the proof of the theorem. □

Additional Results

Lemma 8 (Second order terms for modified treatment policies)**.** *Let* $\mathrm{d}\xi(o)$ *denote* $\mathrm{d}\nu(a,l,z)\mathrm{d}\mathsf{P}(w)$*, and let* $\mathsf{r}(z\mid, a, w)$ *denote* $\mathsf{p}(z \mid a, w)$*, and let* $\mathsf{h}(z\mid, w)$ *denote* $\mathsf{p}(z \mid w)$*. Let* $d(a,w)$ *denote a modified treatment policy satisfying A6. We have*

$$\mathsf{P}D^1_{\eta_1,\delta} - \psi_1(\delta) = \int \left(\frac{\mathsf{g}}{\mathsf{g}_1}\frac{\mathsf{d}}{\mathsf{d}_1} - 1\right)(\mathsf{m} - \mathsf{m}_1)\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi \tag{4.25}$$

$$- \int \left(\frac{\mathsf{g}}{\mathsf{g}_1} - 1\right)(\bar{\mathsf{u}}_1 - \bar{\mathsf{u}})\mathsf{g}_{\delta,1}\mathrm{d}\xi \tag{4.26}$$

$$+ \int \left(\frac{\mathsf{g}}{\mathsf{g}_1} - 1\right)(\mathsf{m}_1 - \mathsf{m})\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi \tag{4.27}$$

$$- \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{b}_1 - \mathsf{b})(\mathsf{v}_1 - \mathsf{v})\mathsf{g}_{\delta,1}\mathrm{d}\xi \tag{4.28}$$

$$- \int (\bar{\mathsf{u}}_1 - \bar{\mathsf{u}})(\mathsf{g}_{\delta,1} - \mathsf{g}_\delta)\mathrm{d}\xi \tag{4.29}$$

and

$$\begin{aligned}\mathsf{P}D^2_{\eta_1,\delta} - \psi_2(\delta) = &\int \left(\frac{\mathsf{e}}{\mathsf{e}_1}\frac{\mathsf{d}}{\mathsf{d}_1} - 1\right)(\mathsf{m} - \mathsf{m}_1)\mathsf{b}_1\mathsf{h}\mathsf{g}_{\delta,1}\mathrm{d}\xi \\ &+ \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{b}_1 - \mathsf{b})(\mathsf{s}_1 - \mathsf{s})\mathsf{g}_{\delta,1}\mathrm{d}\xi \\ &- \int (\mathsf{q}_1 - \mathsf{q})(\mathsf{g}_{\delta,1} - \mathsf{g}_\delta)\mathrm{d}\xi.\end{aligned}$$

Proof Note that

$$
\begin{aligned}
\mathsf{P}S^1_{\eta_1,\delta} - \psi_1(\delta) &= \int \left(\frac{\mathsf{g}}{\mathsf{g}_1}\frac{\mathsf{d}}{\mathsf{d}_1} - 1\right)(\mathsf{m}-\mathsf{m}_1)\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi + \int (\mathsf{m}-\mathsf{m}_1)\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad - \int \bar{\mathsf{u}}(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi - \int \bar{\mathsf{u}}\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad + \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{b}-\mathsf{b}_1)\mathsf{v}_1\mathsf{g}_{\delta,1}\mathrm{d}\xi + \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{u}_1\mathsf{r} - \bar{\mathsf{u}}_1)\mathsf{g}_{\delta,1}\mathrm{d}\xi + \int \bar{\mathsf{u}}_1\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&= (4.25) + \int (\bar{\mathsf{u}}_1 - \bar{\mathsf{u}})\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad + \int (\mathsf{m}-\mathsf{m}_1)\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi + \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{b}-\mathsf{b}_1)\mathsf{v}_1\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad + \int \frac{\mathsf{g}}{\mathsf{g}_1}\mathsf{u}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi - \int \frac{\mathsf{g}}{\mathsf{g}_1}\bar{\mathsf{u}}_1\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad - \int \bar{\mathsf{u}}(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi \\
&= (4.25) - \int \left(\frac{\mathsf{g}}{\mathsf{g}_1} - 1\right)(\bar{\mathsf{u}}_1 - \bar{\mathsf{u}})\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad + \int \frac{\mathsf{g}}{\mathsf{g}_1}\mathsf{m}_1\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi - \int \frac{\mathsf{g}}{\mathsf{g}_1}\mathsf{m}\mathsf{b}\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad + \int (\mathsf{m}-\mathsf{m}_1)\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi + \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{b}-\mathsf{b}_1)\mathsf{v}_1\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad - \int \bar{\mathsf{u}}(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi \\
&= (4.25) - (4.26) \\
&\quad + \int (\mathsf{m}-\mathsf{m}_1)\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi + \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{b}-\mathsf{b}_1)\mathsf{v}_1\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad + \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{m}_1\mathsf{b}_1 + \mathsf{m}\mathsf{b}_1 - \mathsf{m}\mathsf{b}_1 - \mathsf{m}\mathsf{b})\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad - \int \bar{\mathsf{u}}(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi \\
&= (4.25) - (4.26) \\
&\quad + \int (\mathsf{m}-\mathsf{m}_1)\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi + \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{b}-\mathsf{b}_1)\mathsf{v}_1\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad + \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{m}_1-\mathsf{m})\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi + \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{b}_1-\mathsf{b})\mathsf{m}\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&\quad - \int \bar{\mathsf{u}}(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi \\
&= (4.25) - (4.26) + (4.27) - (4.28) \\
&\quad - \int \bar{\mathsf{u}}(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi.
\end{aligned}
\tag{4.30}
$$

Using A6 we can change variables to obtain

$$\mathsf{P}S^{A,1}_{\eta_1,\delta} = \int \bar{\mathsf{u}}_1(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi.$$

The proof for ψ_2 is analogous. This completes the proof of the theorem. □

Lemma 9 (Second order terms for exponential tilting.)**.** *Define* $c(w) = \{\int_a \exp(\delta a)\mathsf{g}(a \mid w)\}^{-1}$, *and let* $c_1(w)$ *be defined analogously. Let* $b(a) = \exp(\delta a)$. *Using the same notation as in Lemma 6, we have*

$$\begin{aligned}
\mathsf{P}D^1_{\eta_1,\delta} - \psi_1(\delta) = &\int \left(\frac{\mathsf{g}}{\mathsf{g}_1}\frac{\mathsf{d}}{\mathsf{d}_1} - 1\right)(\mathsf{m} - \mathsf{m}_1)\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&- \int \left(\frac{\mathsf{g}}{\mathsf{g}_1} - 1\right)(\bar{\mathsf{u}}_1 - \bar{\mathsf{u}})\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&+ \int \left(\frac{\mathsf{g}}{\mathsf{g}_1} - 1\right)(\mathsf{m}_1 - \mathsf{m})\mathsf{b}_1\mathsf{r}\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&- \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{b}_1 - \mathsf{b})(\mathsf{v}_1 - \mathsf{v})\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&+ \int (\bar{\mathsf{u}}_1 - \bar{\mathsf{u}})(\mathsf{g}_{\delta,1} - \mathsf{g}_\delta)\mathrm{d}\xi \\
&- \int \left\{(c_1 - c)^2 \int b\mathsf{g}_1\bar{\mathsf{u}}_1\mathrm{d}\kappa \int b\mathsf{g}\mathrm{d}\kappa\right\}\mathrm{d}\xi \\
&+ \int \left\{(c_1 - c)\int b\bar{\mathsf{u}}_1(\mathsf{g} - \mathsf{g}_1)\mathrm{d}\kappa\right\}\mathrm{d}\xi,
\end{aligned}$$

and

$$\begin{aligned}
\mathsf{P}D^2_{\eta_1,\delta} - \psi_2(\delta) = &\int \left(\frac{\mathsf{e}}{\mathsf{e}_1}\frac{\mathsf{d}}{\mathsf{d}_1} - 1\right)(\mathsf{m} - \mathsf{m}_1)\mathsf{b}_1\mathsf{h}\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&+ \int \frac{\mathsf{g}}{\mathsf{g}_1}(\mathsf{b}_1 - \mathsf{b})(\mathsf{s}_1 - \mathsf{s})\mathsf{g}_{\delta,1}\mathrm{d}\xi \\
&- \int (\mathsf{q}_1 - \mathsf{q})(\mathsf{g}_{\delta,1} - \mathsf{g}_\delta)\mathrm{d}\xi \\
&- \int \left\{(c_1 - c)^2 \int b\mathsf{g}_1\bar{\mathsf{q}}_1\mathrm{d}\kappa \int b\mathsf{g}\mathrm{d}\kappa\right\}\mathrm{d}\xi \\
&+ \int \left\{(c_1 - c)\int b\bar{\mathsf{q}}_1(\mathsf{g} - \mathsf{g}_1)\mathrm{d}\kappa\right\}\mathrm{d}\xi.
\end{aligned}$$

Proof In this proof, (4.30) is also valid. We have

$$\mathsf{P}S^{1,A}_{\eta_1,\delta} - \int \bar{\mathsf{u}}(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi = \mathsf{P}S^{1,A}_{\eta_1,\delta} - \int \bar{\mathsf{u}}_1(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi + \int (\bar{\mathsf{u}}_1 - \bar{\mathsf{u}})(\mathsf{g}_{\delta,1} - \mathsf{g}_\delta)\mathrm{d}\xi$$

It thus remains to prove that

$$\mathsf{P}S^{1,A}_{\eta_1,\delta} - \int \bar{\mathsf{u}}_1(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi = -\int \left\{(c_1 - c)^2 \int b\mathsf{g}_1\bar{\mathsf{u}}_1\mathrm{d}\kappa \int b\mathsf{g}\mathrm{d}\kappa\right\}\mathrm{d}\xi + \int \left\{(c_1 - c)\int b\bar{\mathsf{u}}_1(\mathsf{g} - \mathsf{g}_1)\mathrm{d}\kappa\right\}\mathrm{d}\xi.$$

We have

$$\begin{aligned}
&\mathsf{P}S^{1,A}_{\eta_1} - \int \bar{\mathsf{u}}_1(\mathsf{g}_\delta - \mathsf{g}_{\delta,1})\mathrm{d}\xi \\
&= \int \left\{\int \frac{\mathsf{g}_{1,\delta}}{\mathsf{g}_1}\bar{\mathsf{u}}_1\mathsf{g}\mathrm{d}\kappa - \int \frac{\mathsf{g}_{1,\delta}}{\mathsf{g}_1}\mathsf{g}\mathrm{d}\kappa \int \bar{\mathsf{u}}_1\mathsf{g}_{1,\delta}\mathrm{d}\kappa + \int (\mathsf{g}_{1,\delta} - \mathsf{g}_\delta)\bar{\mathsf{u}}_1\mathrm{d}\kappa\right\}\mathrm{d}\xi \\
&= \int \left\{\frac{\mathsf{g}_{1,\delta}}{\mathsf{g}_1}\mathsf{g}\bar{\mathsf{u}}_1\mathrm{d}\kappa - \int \mathsf{g}_\delta\bar{\mathsf{u}}_1\mathrm{d}\kappa + \int \mathsf{g}_{1,\delta}\bar{\mathsf{u}}_1\mathrm{d}\kappa\left[1 - \int \frac{\mathsf{g}_{1,\delta}}{\mathsf{g}_1}\mathsf{g}\mathrm{d}\kappa\right]\right\}\mathrm{d}\xi \\
&= \int \left\{c_1\int b\bar{\mathsf{u}}_1\mathsf{g}\mathrm{d}\kappa - c_1\int b\bar{\mathsf{u}}_1\mathsf{g}\mathrm{d}\kappa + c_1\int b\mathsf{g}\bar{\mathsf{u}}_1\mathrm{d}\kappa \int (c - c_1)b\mathsf{g}\mathrm{d}\kappa\right\}\mathrm{d}\xi \\
&= \int (c_1 - c)\left\{\int b\bar{\mathsf{u}}_1\mathsf{g}\mathrm{d}\kappa - c_1\int b\mathsf{g}_1\bar{\mathsf{u}}_1\mathrm{d}\kappa\int b\mathsf{g}\mathrm{d}\kappa\right\}\mathrm{d}\xi \\
&= \int (c_1 - c)\left\{\int b\bar{\mathsf{u}}_1\mathsf{g}\mathrm{d}\kappa - c\int b\mathsf{g}_1\bar{\mathsf{u}}_1\mathrm{d}\kappa\int b\mathsf{g}\mathrm{d}\kappa - (c_1 - c)\int b\mathsf{g}_1\bar{\mathsf{u}}_1\mathrm{d}\kappa\int b\mathsf{g}\mathrm{d}\kappa\right\}\mathrm{d}\xi \\
&= \int \left\{-(c_1 - c)^2\int b\mathsf{g}_1\bar{\mathsf{u}}_1\mathrm{d}\kappa\int b\mathsf{g}\mathrm{d}\kappa + (c_1 - c)\left[\int b\bar{\mathsf{u}}_1\mathsf{g}\mathrm{d}\kappa - \int b\mathsf{g}_1\bar{\mathsf{u}}_1\mathrm{d}\kappa\right]\right\}\mathrm{d}\xi \quad (4.31) \\
&= \int \left\{-(c_1 - c)^2\int b\mathsf{g}_1\bar{\mathsf{u}}_1\mathrm{d}\kappa\int b\mathsf{g}\mathrm{d}\kappa + (c_1 - c)\int b\bar{\mathsf{u}}_1(\mathsf{g} - \mathsf{g}_1)\mathrm{d}\kappa\right\}\mathrm{d}\xi,
\end{aligned}$$

where (4.31) follows from $c\int b\mathsf{g}\mathrm{d}\kappa = 1$. The proof for ψ_2 is analogous. □

Chapter 5

Open Source Software for Causal Inference

5.1 Towards "Really Reproducible" Research

Electronic computation has had a transformative impact on the discipline of statistics, both in the development of novel statistical methodology and the practice of statistical data analysis. Modern statistical techniques rely heavily upon the widespread availability of personal computers and high-performance computing systems, and, today, some of the most well-known and influential procedures for statistical estimation and inference — including ensemble machine learning [193, 17, 176], the jackknife [46], and the bootstrap [46, 47, 33] — presume the availability of significant computational resources. The ease of access to and reliability of modern computing systems, coupled with their ever-increasing capabilities, has allowed tremendous strides in not only how statistical methods are developed but in the range of scientific problems to which they may be applied. Despite these advances, critical lessons and pratices for facilitating the reproducibility of findings from the computational sciences, readily absorbed by allied disciplines, were left largely unheeded by statisticians for most of the twentieth and early twenty-first centuries.

An early call to embrace computing and programming was issued by Tukey [165], who saw such activities as critical to the next generation of developments in statistical data analysis. While Tukey's prominence afforded his timely concerns visibility, only a very small fraction of the total academic effort in statistics research became concentrated upon the inception and improvement of standards for statistical programming, computing, and graphics [7, 8, 86] or on the complementary paradigms of literate programming [96] and literate computing [125]. Cross-talk between statistics and related computationally intensive sciences led to further concern about the state of reproducibility in computational research. For example, as lessons learned from their development of *Wavelab*, a robust software toolkit for wavelet analysis, Buckheit and Donoho [21] bemoaned the lack of availability of scientific software, remarking that the "release of software underlying

scientific publication is the exception rather than the rule" while simultaneously observing that, with respect to scientific publications, "the actual scholarship is the complete software development environment and the complete set of instructions which generated the figures." Fortunately, the decades leading to the recent emergence of the interdisciplinary field of data science [43] have been marked by a renewed and fervent interest in open source software development and reproducible research.

As we move into an era in which sophisticated statistical techniques are routinely deployed for rigorously evaluating scientific claims of global concern, such as the vaccine efficacy trials discussed in Chapters 2 and 3, the availability and adoption of robust statistical software will undoubtedly play a central role in enhancing the transparency inherent to the scientific process. That is, the conscientious use of modern statistical methodology alone has become insufficient for the practice of open science. For transparent scientific practice to thrive, user-friendly software will need to become the norm, rather than the exception, as has historically been the case [158, 132]. Such software is characterized by at least five essential characteristics.

1. Clear, easily accessible, highly detailed documentation of all code-derived interfaces and objects, whether developer-oriented or user-facing.
2. Rigorous and focused testing to assess programmatic procedures (e.g., functions, classes, methods) and data structures (e.g., the ubiquitous data frame).
3. In-depth examples using literate programming documents that blend executable code with prose (e.g., `RMarkdown` [197]) or literate computing notebooks that promote the interactive development of computation *informed by data* (e.g., Jupyter notebooks [95, 64]).
4. Open source development, embodying an ongoing, continuous, public peer review of the research product.
5. The automated, near-constant monitoring of software quality through continuous integration services, ensuring accessibility across diverse computer systems and architectures.

By displaying these characteristics, software for statistics can empower the scientific community — and possibly even the public at large — to directly access the published results of scientific investigations. Practices for reproducible research in statistics and allied computational sciences have been the subject of much discussion [e.g., 123, 124, 156, 93, 110]; however, in many academic circles, the core aspects of software development are still viewed as an ancillary activity, rather than as a primary pursuit.

As the fields of statistics and data science continue to co-develop in the coming decades, statisticians will be challenged by questions that highlight the importance of software to the field. Such questions include, for example, (1) how a theorem, or similar mathematical result, can significantly

impact science *except through software*, or (2) in what ways software implementations can readily reveal important insights about the computational bottlenecks of newly developed statistical methodology. Recalling an anecdote of Buckheit and Donoho [21], we note that, without continued investment in the development and promotion of open source software standards, "a year [will continue to be] a long time in this business," as the application of existing statistical methodology to newly procured datasets will be marked by the unreliability and instability of accompanying software. We hope that such occurrences will become exceedingly rare. To that end, we next present three open source software packages, each developed to implement distinct statistical methods described in this greater body of work. Written for the `R` programming language [133], the unrestricted source code for each package is available on the collaborative programming platform GitHub; moreover, each package is accompanied by online documentation, a suite of unit tests, and automated quality control through continuous integration services.

5.2 The `txshift` `R` Package

Summary

Statistical causal inference has traditionally focused on effects defined by inflexible static interventions, applicable only to binary or categorical exposures. The evaluation of such interventions is often plagued by many problems, both theoretical (e.g., non-identification) and practical (e.g., positivity violations); however, stochastic interventions provide a promising solution to these fundamental issues [38]. The `txshift` `R` package provides researchers in (bio)statistics, epidemiology, health policy, economics, and related disciplines with access to state-of-the-art statistical methodology for evaluating the causal effects of stochastic shift interventions on *continuous-valued* exposures. `txshift` estimates the causal effects of modified treatment policies (or "feasible interventions"), which take into account the natural value of an exposure in assigning an intervention level. To accommodate use in study designs incorporating outcome-dependent two-phase sampling (e.g., case-control), the package provides two types of modern corrections, both rooted in semiparametric theory, for constructing unbiased and efficient estimates, despite the significant limitations induced by such designs. Thus, `txshift` makes possible the estimation of the causal effects of stochastic interventions in experimental and observational study settings subject to real-world design limitations that commonly arise in modern scientific practice.

Statement of Need

Researchers seeking to build upon or apply cutting-edge statistical approaches for causal inference often face significant obstacles: such methods are usually not accompanied by robust, well-tested, and well-documented software packages. Yet coding such methods from scratch is often impractical for the applied researcher, as understanding the theoretical underpinnings of these methods requires advanced training, severely complicating the assessment and testing of bespoke causal inference software. What's more, even when such software tools exist, they are usually minimal implementations, providing support only for deploying the statistical method in problem settings untouched by the complexities of real-world data. The `txshift` `R` package solves this problem by providing an open source tool for evaluating the causal effects of flexible, stochastic interventions, applicable to categorical or continuous-valued exposures, while providing corrections for appropriately handling data generated by commonly used but complex two-phase sampling designs.

Background

Causal inference has traditionally focused on the effects of static interventions, under which the magnitude of the exposure is set to a fixed, prespecified value for each unit. The evaluation of such interventions faces a host of issues, among them non-identification, violations of the assumption of positivity, and inefficiency. Stochastic interventions provide a promising solution to these fundamental issues by allowing for the target parameter to be defined as the mean counterfactual outcome under a hypothetically shifted version of the observed exposure distribution [37]. Modified treatment policies, a particular class of such interventions, may be interpreted as shifting the natural exposure level at the level of a given observational unit [68, 38].

Despite the promise of such advances in causal inference, real data analyses are often further complicated by economic constraints, such as when the primary variable of interest is far more expensive to collect than auxiliary covariates. Two-phase sampling is often used to bypass these limitations — unfortunately, these sampling schemes produce side effects that require further adjustment when formal statistical inference is the principal goal of a study. Among the rich literature on two-phase designs, Rose and van der Laan [143] stand out for providing a study of nonparametric efficiency theory under a broad class of two-phase designs. Their work provides guidance on constructing efficient estimators of causal effects under general two-phase sampling designs.

`txshift`'s Scope

Building on these prior works, Hejazi et al. [78] outlined a novel approach for use in such settings: augmented targeted minimum loss (TML) and one-step estimators for the causal effects of

stochastic interventions, with guarantees of consistency, efficiency, and multiple robustness despite the presence of two-phase sampling. These authors further outlined a technique that summarizes the effect of shifting an exposure variable on the outcome of interest via a nonparametric working marginal structural model, analogous to a dose-response analysis. The `txshift` software package, for the `R` language and environment for statistical computing [133], implements this methodology.

`txshift` is designed to facilitate the construction of TML and one-step estimators of the causal effects of modified treatment policies that shift the observed exposure value up (or down) by an arbitrary scalar δ, which may possibly take into account the natural value of the exposure (and, in future versions, the covariates). The `R` package includes tools for deploying these efficient estimators under outcome-dependent two-phase sampling designs, with two types of corrections: (1) a reweighting procedure that introduces inverse probability of censoring weights directly into relevant loss functions, as discussed in Rose and van der Laan [143]; as well as (2) an augmented efficient influence function estimating equation, studied more thoroughly by Hejazi et al. [78]. `txshift` integrates with the `sl3` package [31] to allow for ensemble machine learning to be leveraged in the estimation of nuisance parameters. What's more, the `txshift` package draws on both the `hal9001` [30, 75] and `haldensify` [74] `R` packages to allow each of the efficient estimators to be constructed in a manner consistent with the methodological and theoretical advances of Hejazi et al. [78], which require fast convergence rates of nuisance parameters to their true counterparts for efficiency of the resultant estimator.

Availability

The `txshift` package has been made publicly available both via GitHub (`https://github.com/nhejazi/txshift`) and the Comprehensive `R` Archive Network (`https://CRAN.R-project.org/package=txshift`). Use of the `txshift` package has been extensively documented in the package's `README`, two vignettes, and its `pkgdown` documentation website (`https://code.nimahejazi.org/txshift`).

5.3 The `medshift` `R` Package

Background

This `R` package aims to provide tools for assessing the population intervention direct effect and the population intervention indirect effect, based on the effect decomposition of the population intervention effect introduced in Díaz and Hejazi [35].

To proceed, we will use as our running example a simple data set from an observational study of the relationship between BMI and kids behavior, distributed as part of the `mma` `R` package on the Comprehensive `R` Archive Netowrk (https://CRAN.R-project.org/package=mma). First, a bit of quick programmatic housekeepking for this data example.

```
# preliminaries
library(data.table)
library(dplyr)
library(tidyr)
library(sl3)
library(medshift)
library(mma)
```

The documentation for the data set describes it as a "database obtained from the Louisiana State University Health Sciences Center, New Orleans, by Dr. Richard Scribner. He explored the relationship between BMI and kids behavior through a survey at children, teachers and parents in Grenada in 2014. This data set includes 691 observations and 15 variables."

Unfortunately, the data set contains a few observations with missing values. As these are unrelated to the object of our analysis, we'll simply remove these for the time being. Note that in a real data analysis, we might consider strategies to fully make of the observed data, perhaps by imputing missing values. For now, we simply remove the incomplete observations, resulting in a data set with fewer observations (now 567 units) but otherwise the same structure as the original.

```
# load and clean up data
data(weight_behavior)
weight_behavior_complete <- weight_behavior %>%
  drop_na() %>%
  mutate(as.numeric(sports) - 1)
dim(weight_behavior_complete)
head(weight_behavior_complete)
```

```
##        bmi  age sex  race numpeople car gotosch snack tvhours
   cmpthours
## 1 18.20665 12.2   F OTHER         5   3       2     1       4
           0
## 2 22.78401 12.8   M OTHER         4   3       2     1       4
           2
## 4 25.56754 12.1   M OTHER         2   3       2     1       0
           2
```

```
## 5 15.07408 12.3   M OTHER         4   1       2     1       2
           1
## 6 22.98338 11.8   M OTHER         4   1       1     1       4
           3
## 8 19.15658 12.1   F OTHER         3   3       2     1       0
           0
##   cellhours sports exercises sweat overweigh
## 1         0      1         2     1         0
## 2         0      0         8     2         0
## 4         0      1         9     1         1
## 5         3      0        12     1         0
## 6         2      0         1     1         0
## 8         1      0         1     3         0
```

For the analysis of this observational data set, we focus on the effect of participating in a sports team (`sports`) on the BMI of children (`bmi`), taking several related covariates as mediators (`snack`, `exercises`, `overweigh`) and all other collected covariates as potential confounders. Considering an NPSEM, we separate the observed variables from the data set into their corresponding nodes as follows.

```
Y <- weight_behavior_complete$bmi
A <- weight_behavior_complete$sports
Z <- weight_behavior_complete %>%
  select(snack, exercises, overweigh)
W <- weight_behavior_complete %>%
  select(age, sex, race, numpeople, car, gotosch, tvhours, cmpthours,
         cellhours, sweat)
```

Finally, in our analysis, we consider an incremental propensity score intervention (IPSI), as first proposed by Kennedy et al. [92], wherein the *odds of participating in a sports team* is modulated by a fixed amount ($0 \leq \delta \leq \infty$), specified *a priori*, for each individual. Such an intervention may be interpreted as the effect of a school program that motivates children to participate in sports teams. To exemplify our approach, we postulate a motivational intervention that *triples the odds* of participating in a sports team for each individual:

```
delta_shift_ipsi <- 3
```

To easily incorporate ensemble machine learning into the estimation procedure, we rely on the facilities provided in the `sl3` `R` package (`https://tlverse.org/sl3`) [31]. We construct an ensemble learner using a handful of popular machine learning algorithms below.

```
# SL learners used for continuous data (nuisance parameter M)
xgb_contin_lrnr <- Lrnr_xgboost$new(
  nrounds = 50, objective = "reg:linear"
)
enet_contin_lrnr <- Lrnr_glmnet$new(
  alpha = 0.5, family = "gaussian", nfolds = 3
)
lasso_contin_lrnr <- Lrnr_glmnet$new(
  alpha = 1, family = "gaussian", nfolds = 3
)
fglm_contin_lrnr <- Lrnr_glm_fast$new(family = gaussian())
contin_lrnr_lib <- Stack$new(
  enet_contin_lrnr, lasso_contin_lrnr,
  fglm_contin_lrnr, xgb_contin_lrnr
)
sl_contin_lrnr <- Lrnr_sl$new(
  learners = contin_lrnr_lib,
  metalearner = Lrnr_nnls$new()
)
# SL learners used for binary data (nuisance parameters G and E)
xgb_binary_lrnr <- Lrnr_xgboost$new(
  nrounds = 50, objective = "reg:logistic"
)
enet_binary_lrnr <- Lrnr_glmnet$new(
  alpha = 0.5, family = "binomial", nfolds = 3
)
lasso_binary_lrnr <- Lrnr_glmnet$new(
  alpha = 1, family = "binomial", nfolds = 3
)
fglm_binary_lrnr <- Lrnr_glm_fast$new(family = binomial())
binary_lrnr_lib <- Stack$new(
  enet_binary_lrnr, lasso_binary_lrnr,
  fglm_binary_lrnr, xgb_binary_lrnr
)
logistic_metalearner <- make_learner(
  Lrnr_solnp, metalearner_logistic_binomial, loss_loglik_binomial
)
sl_binary_lrnr <- Lrnr_sl$new(
```

```
  learners = binary_lrnr_lib,
  metalearner = logistic_metalearner
)
```

Population Intervention Effect Decomposition

We may decompose the population intervention effect (PIE) in terms of a *population intervention direct effect* (PIDE) and a *population intervention indirect effect* (PIIE):

$$\overbrace{\mathbb{E}\{Y(A_\delta, Z(A_\delta)) - Y(A_\delta, Z)\}}^{\text{PIIE}} + \overbrace{\mathbb{E}\{Y(A_\delta, Z) - Y(A, Z)\}}^{\text{PIDE}}.$$

This decomposition of the PIE as the sum of the population intervention direct and indirect effects has an interpretation analogous to the corresponding standard decomposition of the average treatment effect. In the sequel, we will compute each of the components of the direct and indirect effects above using appropriate estimators as follows.

- For $\mathbb{E}\{Y(A, Z)\}$, the sample mean $\frac{1}{n}\sum_{i=1}^{n} Y_i$ is sufficient;
- for $\mathbb{E}\{Y(A_\delta, Z)\}$, an efficient one-step estimator for the effect of a joint intervention altering the exposure mechanism but not the mediation mechanism, as proposed in Díaz and Hejazi [35]; and,
- for $\mathbb{E}\{Y(A_\delta, Z_{A_\delta})\}$, an efficient one-step estimator for the effect of a joint intervention on both the exposure and and mediator(s), as proposed in Kennedy et al. [92] and implemented in the `npcausal` `R` package (https://github.com/ehkennedy/npcausal).

Estimating the Effect Decomposition Term

As given in Díaz and Hejazi [35], the statistical functional identifying the decomposition term that appears in both the PIDE and PIIE $\mathbb{E}\{Y(A_\delta, Z)\}$, which corresponds to altering the exposure mechanism while keeping the mediation mechanism fixed, is

$$\theta_0(\delta) = \int m_0(a, z, w) g_{0,\delta}(a \mid w) p_0(z, w) d\nu(a, z, w),$$

for which a one-step estimator is available. The corresponding *efficient influence function* (EIF) with respect to the nonparametric model $\mathcal{M}$ is $D_{\eta,\delta}(o) = D^{Y}_{\eta,\delta}(o) + D^{A}_{\eta,\delta}(o) + D^{Z,W}_{\eta,\delta}(o) - \theta(\delta)$. The one-step estimator may be computed using the EIF estimating equation, making use of cross-fitting [199, 25] to circumvent any need for entropy conditions (i.e., Donsker class restrictions).

The resultant estimator is

$$\hat{\theta}(\delta) = \frac{1}{n}\sum_{i=1}^{n} D_{\hat{\eta}_{j(i)},\delta}(O_i) = \frac{1}{n}\sum_{i=1}^{n}\left\{D^{Y}_{\hat{\eta}_{j(i)},\delta}(O_i) + D^{A}_{\hat{\eta}_{j(i)},\delta}(O_i) + D^{Z,W}_{\hat{\eta}_{j(i)},\delta}(O_i)\right\},$$

which is implemented in the `medshift R` package. We make use of that implementation to estimate $\mathbb{E}\{Y(A_\delta, Z)\}$ via its one-step estimator $\hat{\theta}(\delta)$, as demonstrated below.

```
# let's compute the parameter where A (but not Z) are shifted
theta_eff <- medshift(
  W = W, A = A, Z = Z, Y = Y,
   delta = delta_shift_ipsi,
   g_learners = sl_binary_lrnr,
   e_learners = sl_binary_lrnr,
   m_learners = sl_contin_lrnr,
   phi_learners = Lrnr_hal9001$new(),
   estimator = "onestep",
   estimator_args = list(cv_folds = 3)
)
summary(theta_eff)
```

Estimating the Direct Effect

Recall that, based on the decomposition outlined previously, the population intervention direct effect may be denoted $\beta_{\text{PIDE}}(\delta) = \theta_0(\delta) - \mathbb{E}Y$. Thus, an estimator of the PIDE, $\hat{\beta}_{\text{PIDE}}(\delta)$ may be expressed as a composition of estimators of its constituent parameters:

$$\hat{\beta}_{\text{PIDE}}(\delta) = \hat{\theta}(\delta) - \frac{1}{n}\sum_{i=1}^{n} Y_i.$$

Based on the above, we may construct an estimator of the PIDE using quantities already computed. The convenience function below applies the simple delta method required in the case of a linear contrast between the two constituent parameters:

```
# convenience function to compute inference via delta method: EY1 - EY0
linear_contrast <- function(params, eifs, ci_level = 0.95) {
  # bounds for confidence interval
  ci_norm_bounds <- c(-1, 1) * abs(qnorm(p = (1 - ci_level) / 2))
  param_est <- params[[1]] - params[[2]]
  eif <- eifs[[1]] - eifs[[2]]
  se_eif <- sqrt(var(eif) / length(eif))
```

```
  param_ci <- param_est + ci_norm_bounds * se_eif
  # parameter and inference
  out <- c(param_ci[1], param_est, param_ci[2])
  names(out) <- c("lwr_ci", "param_est", "upr_ci")
  return(out)
}
```

With the above convenience function in hand, we'll construct or extract the necessary components from existing objects and simply apply the function:

```
# parameter estimates and EIFs for components of direct effect
EY <- mean(Y)
eif_EY <- Y - EY
params_de <- list(theta_eff$theta, EY)
eifs_de <- list(theta_eff$eif, eif_EY)

# direct effect = EY - estimated quantity
de_est <- linear_contrast(params_de, eifs_de)
de_est
##       lwr_ci    param_est       upr_ci
##      -0.4961   -0.0073         0.4815
```

As given above, we have for our estimate of the direct effect $\hat{\beta}_{\text{PIDE}}(\delta) = -0.007$.

5.4 The `haldensify` R Package

Statement of Need

In causal inference problems, both classical estimators (e.g., based on inverse probability weighting) and doubly robust estimators (e.g., one-step estimation, targeted minimum loss estimation) require estimation of the propensity score, a nuisance parameter corresponding to the treatment mechanism. While exposures of interest may often be continuous-valued, most approaches opt to discretize the exposure so as to estimate effects based on categorical exposures — such a simplification is often done out of convenience, to avoid estimation of the *generalized propensity score* [81, 88], which is a conditional density function. The `haldensify` package introduces a flexible approach for estimating such conditional density functions, using the highly adaptive lasso (HAL), a nonparametric regression function that has been proven to converge to a given target function(al) at $n^{-1/3}$-rate under minimal conditions.

Consider data generated by typical cohort sampling $O = (W, A, Y)$, where W is a vector of baseline covariates, A is a continuous-valued exposure, and Y is an outcome of interest. Estimation of the generalized propensity score $g_{0,A}$ corresponds to estimating the conditional density of A given $W = w$. A simple strategy for estimating this nuisance function is to assume a parametric working model and use parametric regression to generate suitable density estimates. For example, one could operate under the working assumption that A given W follows a normal distribution with homoscedastic variance and mean $\sum_{j=1}^{p} \beta_j \phi_j(W)$, where $\phi = (\phi_j : j)$ are user-selected basis functions and $\beta = (\beta_j : j)$ are unknown regression parameters. In this case, a density estimate would be generated by fitting a linear regression of A on $\phi(W)$ to estimate the conditional mean of A given W, paired with an estimate of the variance of A. Then, the estimated conditional density would be given by the density of a Gaussian distribution evaluated at these estimates. Unfortunately, most such approaches do not allow for flexible modeling of $g_{0,A}$. This motivated our development of a novel and flexible procedure for constructing conditional density estimates $g_{n,A}(a \mid w)$ of A given $W = w$ (possibly subject to observation-level weights), evaluated at $a \in \mathcal{A}$.

Conditional Density Estimation by Pooled Hazard Regression

As consistent estimation of the generalized propensity score is an integral part of constructing estimators of the causal effects of continuous-valued exposures, our conditional density estimator, built around the HAL regression function, may be quite useful in flexibly constructing such estimates. We note that proposals for the data adaptive estimation of such quantities are sparse in the literature [e.g., 201]. Notably, Díaz and van der Laan [39] gave a proposal for constructing semiparametric estimators of such a target quantity based on exploiting the relationship between the hazard and density functions. Our proposal builds upon theirs in several key ways.

1. We adjust their algorithm so as to incorporate sample-level weights, necessary for making use of sample-level weights (e.g., inverse probability of censoring weighting).

2. We replace the use of arbitrary classification models with the highly adaptive lasso.

While our first modification is general and may be applied to the estimation strategy of Díaz and van der Laan [39], our latter contribution requires adjusting the penalization aspect of HAL regression models so as to respect the use of a loss function appropriate for density estimation on the hazard scale.

To build an estimator of a conditional density, Díaz and van der Laan [39] considered discretizing the observed $a \in A$ based on a number of bins T and a binning procedure (e.g., including the same number of points in each bin or forcing bins to be of the same length). We note that the choice of the tuning parameter T corresponds roughly to the choice of bandwidth in classical kernel den-

sity estimation; this will be made clear upon further examination of the proposed algorithm. The data $\{A, W\}$ are reformatted such that the hazard of an observed value $a \in A$ falling in a given bin may be evaluated via standard classification techniques. In fact, this proposal may be viewed as a re-formulation of the classification problem into a corresponding set of hazard regressions:

$$\begin{aligned}\mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid W) =& \mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid A \geq \alpha_{t-1}, W) \\ & \times \prod_{j=1}^{t-1} \{1 - \mathbb{P}(A \in [\alpha_{j-1}, \alpha_j) \mid A \geq \alpha_{j-1}, W)\},\end{aligned}$$

where the probability that a value of $A \in \mathcal{A}$ falls in a bin $[\alpha_{t-1}, \alpha_t)$ may be directly estimated from a standard classification model. The likelihood of this model may be re-expressed in terms of the likelihood of a binary variable in a data set expressed through a repeated measures structure. Specifically, this re-formatting procedure is carried out by creating a data set in which any given observation A_i appears (repeatedly) for as many intervals $[\alpha_{t-1}, \alpha_t)$ that there are prior to the interval to which the observed a belongs. A new binary outcome variable, indicating $A_i \in [\alpha_{t-1}, \alpha_t)$, is recorded as part of this new data structure. With the re-formatted data, a pooled hazard regression, spanning the support of A is then executed. Finally, the conditional density estimator

$$g_{n,\alpha}(A \mid W) = \frac{\mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid W)}{(\alpha_t - \alpha_{t-1})},$$

for $\alpha_{t-1} \leq a \leq \alpha_t$, may be constructed. As part of this procedure, the hazard estimates are mapped to density estimates through rescaling of the estimates by the bin size $(\alpha_t - \alpha_{t-1})$.

In its original proposal, a key element of this procedure was the use of any arbitrary classification procedure for estimating $\mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid W)$, facilitating the incorporation of flexible, data adaptive estimators. We alter this proposal in two ways.

1. Replace the arbitrary estimator of $\mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid W)$ with HAL regression [166, 11, 167], as implemented in the `hal9001 R` package [30, 75].

2. Accommodate the use of sample-level weights, making it possible for the resultant conditional density estimator to achieve a convergence rate with respect to a loss-based dissimilarity of $n^{-1/3}$ [13].

Our procedure alters the HAL regression function to use a loss function tailored for estimation of the hazard, invoking ℓ_1-penalization in a manner consistent with this loss.

Code Demonstration

First, let's load a few required packages, set a seed to make our example reproducible, and generate some very simple, simulated example data.

```
library(haldensify)
library(data.table)
library(ggplot2)
set.seed(75681)

make_example_data <- function(n_obs) {
  W <- runif(n_obs, -4, 4)
  A <- rnorm(n_obs, mean = W, sd = 0.25)
  dat <- as.data.table(list(A = A, W = W))
  return(dat)
}

# number of observations in our simulated dataset
n_obs <- 200
example_data <- make_example_data(n_obs)

# let's take a quick look at the data
head(example_data)
```

```
##             A           W
## 1:  2.3063922  2.24687273
## 2:  0.9297479  0.91025531
## 3: -3.2443382 -2.98696024
## 4: -0.1842217 -0.01204378
## 5:  3.2756387  3.59166824
## 6: -2.9132139 -3.02363838
```

The function `make_example_data()`, defined below, generates a baseline covariate W and a continuous-valued exposure variable A, whose mean is a function of W.

Next, we'll fit our pooled hazards conditional density estimator via the `haldensify()` function. Based on underlying theory and simulation experiments, we recommend setting a relatively large number of bins and using a binning strategy compatible with the large number of bins.

```
haldensify_fit <- haldensify(
  A = example_data[["A"]],
  W = example_data[["W"]],
  n_bins = c(10, 20),
  grid_type = "equal_range",
  lambda_seq = exp(seq(-0.1, -10, length = 500)),
```

```
  # the following are passed to hal9001::fit_hal() internally
  max_degree = 5,
  num_knots = NULL,
  smoothness_orders = 0,
  reduce_basis = 1 / sqrt(n_obs)
)

# print the output object
haldensify_fit

## HAL Conditional Density Estimation
## Number of bins over support of A: 20
## CV-selected lambda: 4e-04
## Summary of fitted HAL:
##         coef                term
##  1:  4.015834         (Intercept)
##  2:  8.219963  [ I(W >= -3.305) ]
##  3:  7.080282  [ I(bin_id >= 9) ]
##  4: -6.906777  [ I(W >= -3.393) ]
##  5:  6.111346  [ I(bin_id >= 7) ]
##  6:  5.984919   [ I(W >= 0.474) ]
##  7:  5.615845  [ I(bin_id >= 2) ]
##  8:  5.536335  [ I(bin_id >= 4) ]
##  9:  5.375681 [ I(bin_id >= 13) ]
## 10:  5.270633  [ I(W >= -0.267) ]
```

Having constructed the conditional density estimator, we can examine the empirical risk over the grid of choices of the ℓ_1 regularization parameter λ. To do this, we can simply call the available `plot()` method, which uses the cross-validated conditional density fit stored in the `haldensify` object. For example,

```
plot(haldensify_fit)
```

The empirical risk curve of the conditional density estimates across differing values of λ are visualized in Figure 18.

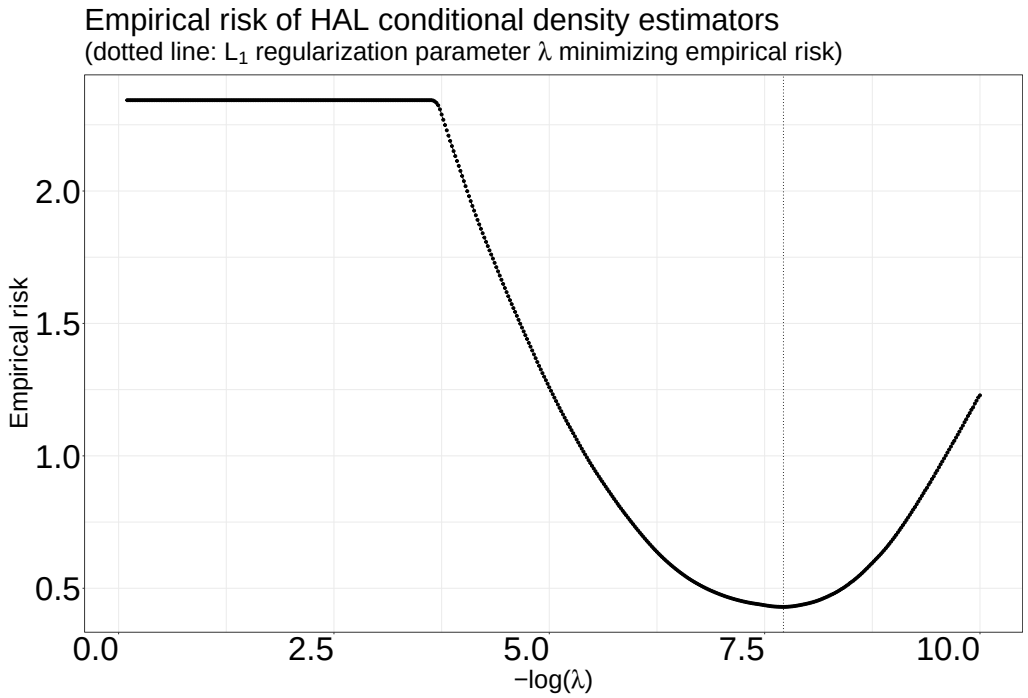

Figure 18: Empirical risk of the estimated conditional density $g_{n,A}$ across a grid in the regularization parameter λ.

Finally, we can predict the conditional density over the grid of observed values A across different elements of the support W. We do this using the `predict()` method of `haldensify` and plot the results below.

```
# predictions to recover conditional density of A|W
new_a <- seq(-4, 4, by = 0.05)
new_dat <- as.data.table(list(
  a = new_a,
  w_neg = rep(-2, length(new_a)),
  w_zero = rep(0, length(new_a)),
  w_pos = rep(2, length(new_a))
))
new_dat[, pred_w_neg := predict(haldensify_fit,
                                new_A = new_dat[["a"]],
                                new_W = new_dat[["w_neg"]])]
new_dat[, pred_w_zero := predict(haldensify_fit,
                                 new_A = new_dat[["a"]],
                                 new_W = new_dat[["w_zero"]])]
```

```
new_dat[, pred_w_pos := predict(haldensify_fit,
                                new_A = new_dat[["a"]],
                                new_W = new_dat[["w_pos"]])]

# visualize results
dens_dat <-  melt(
  new_dat,
  id = c("a"),
  measure.vars = c("pred_w_pos", "pred_w_zero", "pred_w_neg")
)
p_dens <- ggplot(dens_dat, aes(x = a, y = value, colour = variable)) +
  geom_point() +
  geom_line() +
  stat_function(fun = dnorm, args = list(mean = -2, sd = 0.25),
                colour = "blue", linetype = "dashed") +
  stat_function(fun = dnorm, args = list(mean = 0, sd = 0.25),
                colour = "darkgreen", linetype = "dashed") +
  stat_function(fun = dnorm, args = list(mean = 2, sd = 0.25),
                colour = "red", linetype = "dashed") +
  labs(
    x = "Observed value of W",
    y = "Estimated conditional density",
    title = "Conditional density estimates g(A|W)"
  ) +
  theme_bw() +
  theme(legend.position = "none")
p_dens
```

The resulting conditional density estimates are visualzed in Figure 19.

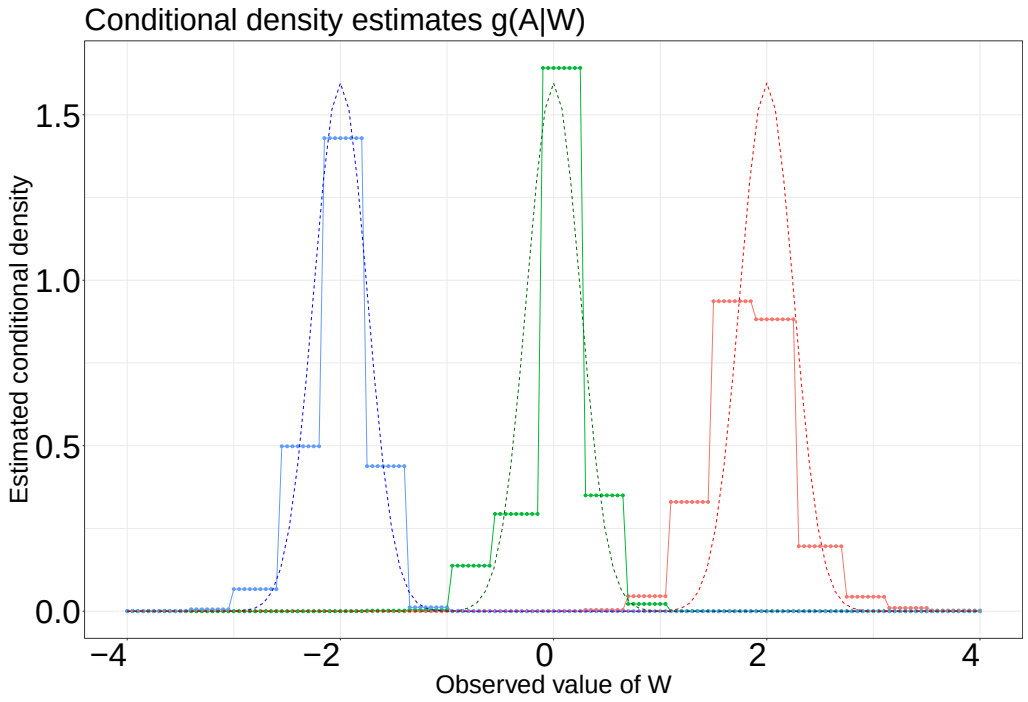

Figure 19: Conditional density estimates evaluated at different values of W, compared to the reference distribution at those same values.

Chapter 6

Directions for Future Investigation

While the presented body of work has provided novel statistical methodology for working with stochastic treatment regimes, there remains much more to do. To motivate future efforts, there is demand for the development of theory, methods, and software for (1) higher-order efficient estimation of novel causal effects, including (in)direct effects; and (2) generalizable, nonparametric estimation of flexible, path-specific causal effects for time-to-event outcomes and outcome-dependent sampling. Such statistical developments are well-positioned to be guided by the pressing scientific necessity of analyzing Phase III COVID-19 vaccine efficacy trials, though myriad other applications will surely emerge as the proposed new class of methodology reaches maturity.

6.1 Pressing New Challenges

Fueled by the deluge of "Big Data" amassed across collaborative research networks, observational studies arm today's scientists with the means to investigate elaborate, albeit daunting, questions. Fortunately, formal causal inference frameworks outline tools for expressing such questions in terms of hypothetical interventions and complex *path-specific* effects [117, 80]. Consider, for example, efficacy trials to evaluate candidate preventive vaccines for COVID-19; the observed data are a sample of random variables O, with distribution P_0, where $O = (W, A, Z, M, Y)$ consists of baseline covariates W (e.g., age, sex, co-morbidities), randomized vaccine v. placebo assignment A, mediating immunologic biomarkers such as binding or neutralizing antibody levels M, mediator-outcome confounders affected by treatment Z (e.g., post-vaccination risky behavior), and symptomatic SARS-CoV-2 infection Y. Two distinct pathways reveal the direct and indirect effects [185] of vaccination: (1) $A \rightarrow Y$, and (2) $A \rightarrow M \rightarrow Y$ for the partial effect through immunologic biomarkers. Causal inference empowers us to investigate how disease risk *would have changed* under counterfactual treatment regimens, defined by interventions set-

ting $A = a$ to $a^\star \in \mathcal{A}$, that propagate to mediators M to yield $M(a^\star) \in \mathcal{M}$. These counterfactual random variables (i.e., $a^\star$ and $M(a^\star)$), with distribution $P_0^\star$, may be used to define highly interpretable causal estimands $\psi_0^\star = \psi(P_0^\star)$ — for example, the natural indirect effect $\psi_0^\star = \mathbb{E}[Y(M(a^\star), a^\star) - Y(M(a), a^\star)]$ [137], quantifying the causal impact of vaccination on disease risk *mediated only through* the immunologic biomarkers M.

Although observational studies have led to a renaissance in statistical causal inference, many significant challenges remain: causal estimands can be "unidentifiable" (i.e., learning $\psi(P_0^\star)$ may be impossible from observed data O), under even mildly non-standard conditions; unfounded parametric assumptions can cause estimation bias, leading to questionable conclusions; and, estimation of the statistical parameter $\psi(P)$ may be complicated by biased sampling and high-dimensional or longitudinal data. Even effect definitions can prove limiting: mediation analysis has focused on natural (in)direct effects, whose identification assumptions preclude intermediate confounding by Z [126, 160, 109, 187]. While data adaptive regression may address parametric model estimation bias, its use necessitates augmented estimators [127, 179, 178, 32] and mathematically intricate derivations [23] on a case-by-case basis for novel causal estimands, motivating the dissemination of robust statistical software. Real-world study designs, such as outcome-dependent two-phase sampling (the norm in immunologic biomarker correlates analyses [70]), require substantial corrections to ensure efficient effect estimation [78] and extensions for complex (e.g., possibly right-censored time-to-event) outcomes.

Vaccine efficacy trials present unlimited yet pressing challenges, from a dire need for path-specific causal estimands robustly identifiable and estimable with right-censored mediators and outcomes to efficiency theory for estimation under novel two-phase sampling designs.

Grounding future research efforts, we briefly review the methodological contributions made thus far, which have leveraged advances in non/semi-parametric causal inference to develop improved statistical estimation techniques as well as new effect definitions extending causal inference approaches to non-standard yet real-world settings.

6.2 Efficient Estimation and Two-Phase Sampling Corrections

Despite significant strides in statistical causal inference with the development of multiply robust non/semi-parametric techniques (e.g., double machine learning [26, 25], targeted minimum loss estimation [180, 179, 178]), classical procedures such as inverse probability weighting (IPW) [84, 144, 80] remain widely used for their ease of implementation across a diversity of settings [80]. Though straightforward, IPW estimators require consistent estimation of a re-weighting mechanism $\mathrm{g}_0(A \mid W)$, used to induce balance on A. Estimates $\mathrm{g}_n(A \mid W)$ are usually obtained via

finite-dimensional parametric models, a practice prone to biasing estimates through model misspecification. While machine learning provides a potential solution, most approaches are inconsistent with efficiency theory, which requires a fast convergence rate ($1/\sqrt[4]{n}$) of the estimate to the true mechanism (typically unattainable by machine learning). We have formulated a novel class of IPW estimators [48] by coupling the highly adaptive lasso [11, 167, 13, 75] with sieve-based selection strategies to achieve guarantees of consistency and non/semi-parametric efficiency without sacrificing flexible estimation of $\mathrm{g}_n(A \mid W)$. Our work is the first demonstration that IPW estimators can successfully incorporate flexible modeling without compromising asymptotic bias or variance, outlining numerous avenues for future investigation. A simple extension of this approach appeared in Chapter 1, in which we developed nonparametric-efficient IPW estimators for the causal effects of stochastic interventions, showing that this class of procedure could work even when g_0 is the conditional density of treatment, instead of the much simpler conditional probability of treatment studied previously.

While non/semi-parametric causal inference can provide interpretable estimands, their estimation is often complicated by the thorny challenges posed by complex study designs. For example, immune correlates analyses of vaccine efficacy trials commonly use outcome-dependent two-phase sampling [70], in which immunologic biomarkers are measured on a subset of study participants based on outcome status (e.g., infection) and on demographic characteristics, severely complicating the statistical estimation problem. Janes et al. [90] followed just such a design in providing the first immune correlates analysis of the HIV Vaccine Trial Network 505 preventive HIV-1 vaccine efficacy trial [67]. Seeking to quantify the causal impact of post-vaccination antibody and T-cell immunologic biomarkers on the risk of HIV-1 infection, in Chapter 2 and Hejazi et al. [78], we fused two disparate literatures on (1) stochastic interventions [155, 37], to adopt a counterfactual framework applicable to continuous-valued immunologic biomarkers, and (2) non/semi-parametric efficiency for two-phase designs [19, 143], to generalize our causal effect estimates beyond the second-phase sample. Our approach allowed for the mean counterfactual HIV-1 infection risk in the HVTN 505 trial to be quantified under hypothetical shifts in the observed immunologic biomarker profile. We developed non/semi-parametric estimators of such causal effect estimands, with guarantees of efficiency and multiple robustness despite two-phase sampling. Using marginal structural models [111], we formulated a dose-response analysis strategy for summarizing the effects of shifting immunogenicity along a pre-specified grid, providing a variable importance measure for ranking immunologic biomarkers as study endpoints in future vaccine trials. In Chapter 3, we showed that an extension of this strategy could be used to study candidate mechanistic correlates of protection in vaccine efficacy trials of COVID-19.

6.3 Robust Causal Mediation for Complex Path Analysis

While interest in path-specific effects dates back to the work of Wright [196], causal mediation analysis came into its modern form only with the definition and identifiability of the natural (in)direct effects [137, 118]. Though the natural (in)direct effects were significant advances, they face several limitations: they cannot accommodate continuous-valued treatments (i.e., $A \in \{0, 1\}$); they are defined by *static* interventions, which deterministically set A to a fixed value a in its support $\mathcal{A}$; their identification requires a restriction on "cross-world" counterfactuals of the mediators M, which is incompatible with randomization; and they are unidentifiable in the presence of mediator-outcome confounders Z affected by treatment A ("intermediate confounders"). All this significantly limits the scope of application of these canonical causal effects. To combat these shortcomings, we developed, in Díaz and Hejazi [35], a path-specific decomposition of the population intervention effect [37] of flexible, stochastic interventions [155, 36, 91], accommodating multivariate M and applicable to categorical or continuous A. Our novel (in)direct effects do not require any cross-world counterfactual independencies, allowing for their implications to be rigorously tested in RCTs. We outlined modern, multiply robust estimators of our (in)direct effects (implemented in our open source `medshift` software package [76]), alongside non/semi-parametric efficiency theory.

Though our developments laid the foundations of a new, general framework for causal mediation analysis, our (in)direct effects, like their natural effect counterparts, could not accommodate intermediate confounders Z, motivating work on "interventional" (in)direct effects [42, 79]. Inteventional (in)direct effects [188, 190] are a new class of causal estimands utilizing joint static and stochastic interventions (to A and M, respectively) to remain identifiable under intermediate confounding. In our initial contribution to the literature on interventional effects, we provided the first detailed developments of efficiency theory and non/semi-parametric efficient estimators for existing interventional (in)direct effects [42] (and the first open source software package, `medoutcon`, for their application [77]). We then expanded upon our new mediation analysis framework by defining the *stochastic* interventional (in)direct effects [79], applicable to categorical or continuous A and identifiable under less restrictive assumptions than their classical counterparts. It remains to generalize such effects to accommodate censored mediators and (possibly time-to-event) outcomes.

6.4 Higher-Order Efficient Estimation of Novel Causal Effects

Several important developments must be pursued in order for study of higher-order efficiency to apply to complex causal effect estimands and their non/semi-parametric estimators.

(a) Theoretical development and evaluation of novel higher-order efficient estimators based on targeted undersmoothing with the highly adaptive lasso regression function.

(b) Higher-order non/semiparametric efficient estimators of the causal direct and indirect effects of stochastic treatment regimes.

(c) Techniques for higher-order efficient estimation under outcome-dependent two-phase sampling designs, readily applicable to immune correlates analyses of COVID-19 and HIV-1 vaccine efficacy trials.

Higher-order efficient estimation of the complex statistical functionals arising in non/semiparametric causal inference is an area largely undeveloped, though the first steps advancing this research program are slowly being taken [135, 23]. Such techniques are desirable for the fact that they expand the nuisance parameter configurations under which multiply robust estimators may attain the non/semi-parametric efficiency bound. In our work constructing nonparametric-efficient IPW estimators [48], we demonstrated that a targeted undersmoothing approach based on the highly adaptive lasso (HAL) could solve a critical component of the estimating equation implied by the efficient influence function (EIF). A significant step in developing this family of approaches for higher-order efficient estimation requires deriving second-order remainder terms $R_2(P, P_0)$ of the EIF Taylor expansion, for example, in problems with flexible stochastic interventions on the treatment A and/or of complex causal (in)direct effect estimands. The formulation of a unique targeted undersmoothing approach to construct HAL nuisance parameter estimators solving the EIF estimating equation and remainder $R_2(P, P_0)$ would constitute a generalizable strategy for higher-order estimation without reliance on specialized knowledge beyond standard non/semiparametric efficiency theory, a significant step past similar recent developments [167, 12]. Like related approaches, our estimators would be equipped with multiply robust confidence intervals, allowing for valid, efficient statistical inference even under nuisance parameter misspecification. Extending our undersmoothing approach to the augmented EIFs implied by outcome-dependent two-phase sampling corrections would allow our higher-order estimators to be applied in statistical analyses of immune correlates in vaccine efficacy trials, through our ongoing collaborations with the COVID-19 Prevention Trials and HIV Vaccine Trials Networks.

6.5 Extending Causal Mediation Analysis to Complex Settings

Causal mediation analysis has proven to be a powerful tool for dissecting the mechanism of particular interventions in well-studied systems; however, the complex data produced by modern studies is largely incompatible with the comparatively simple estimation strategies prominent in mediation analysis. Consequently, several important developments ought to be considered.

(a) Novel decompositions of direct and indirect causal effects as well as their efficient estimation in settings with possibly right-censored time-to-event outcomes and outcome-dependent two-phase sampling.

(b) Robust, novel causal inference transport methodology for bridging these direct and indirect effects to heterogeneous populations (e.g., between vaccine efficacy trials).

(c) Open source software for the adoption of these newly formulated direct and indirect effects in immune correlates analyses of COVID-19 and HIV-1 vaccine efficacy trials.

Biomedical and health studies, vaccine efficacy trials especially, are often complicated by time-to-event outcomes and outcome-dependent two-phase sampling [50] (e.g., case-cohort [130, 5, 107]). A common goal is to ascertain the effect of a treatment, through mediating variables, on the occurrence of a possibly right-censored time-to-event outcome. For example, in immune correlates analyses of vaccine trials [70], the observed data are random variables $X = (W, A, Z, M, \Delta, \widetilde{T})$, where $\widetilde{T} = \min(T, C)$ for failure time T and censoring time C with $\Delta = \mathbb{I}(T \leq C)$ indicating observed failure (other variables remain as previously defined). To assess the indirect effect of vaccination A through immunologic biomarkers M, two innovations are necessary: (1) new path-specific effects identifiable under intermediate confounding and capable of handling time-to-event outcomes, and (2) efficient estimation strategies for outcome-dependent two-phase sampling based on $\widetilde{T}$. For (1), we have proposed flexible (in)direct effect estimands [35, 79], robust to intermediate confounding; however, our (in)direct effects accommodate neither time-to-event outcomes nor censoring. The study of (in)direct effect estimands under such conditions is in its infancy: current strategies [e.g., 159, 200] break down under intermediate confounding or are limited to binary treatments $A \in \{0, 1\}$. For (2), current methods construct second-phase samples based on Δ rather than $\widetilde{T}$, a limitation ignoring the time-to-event nature of the outcome process and constraining sampling efficiency. Generalizing (in)direct effect estimands necessitates methods for bridging estimates to new populations (i.e., external validity); such *causal transport* techniques [122, 121, 4] are under study but variants for path-specific effects [e.g., 149] are in a nascent stage. We will complement our theoretical and methodological pursuits by developing and disseminating open source statistical software and with the application of these approaches in immune correlates analyses of Phase III vaccine trials through our collaborative role in the COVID-19 Prevention Trials Network.

6.6 A Broader Significance: Advancing Science

Since path-specific causal effects are ideal for developing scientific answers to questions of mechanism, my proposed research program will have important bearings on problems across many

fields, from epidemiology and medicine to economics and psychology. In the health and medical sciences, where the measurement of important but costly variables (e.g., immunologic biomarkers) complicates effect estimation, sophisticated methods for handling outcome-dependent two-phase sampling, a key tool in scientific trial design, are sorely needed. I am particularly motivated by avenues for formulating direct and indirect effects applicable to complex data from vaccine efficacy trials and will leverage my collaborations with the COVID-19 Vaccine Prevention Trials and HIV Vaccine Trials Networks to inform scientifically impactful open problems in causal inference. In turn, the methods we develop will help to maximize what we can learn about critical and timely scientific questions, such as how best to tailor future vaccines to mitigate infection risk.

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