Parameterising the effect of a continuous exposure using average derivative effects

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Abstract

The (weighted) average treatment effect is commonly used to quantify the main effect of a binary exposure on an outcome. Extensions to continuous exposures, however, either quantify the effects of interventions that are rarely relevant (e.g., applying the same exposure level uniformly in the population), or consider shift interventions that are rarely intended, raising the question how large a shift to consider. Average derivative effects (ADEs) instead express the effect of an infinitesimal shift in each subject’s exposure level, making inference less prone to extrapolation. ADEs, however, are rarely considered in practice because their estimation usually requires estimation of (a) the conditional density of exposure given covariates, and (b) the derivative of (a) w.r.t. exposure. Here, we introduce a class of estimands which can be inferred without requiring estimates of (a) and (b), but which reduce to ADEs when the exposure obeys a specific distribution determined by the choice of estimand in the class. We moreover show that when the exposure does not obey this distribution, our estimand represents an ADE w.r.t. an ‘intervention’ exposure distribution. We identify the ‘optimal’ estimand in our class and propose debiased machine learning estimators, by deriving influence functions under the nonparametric model.

Keywords: Observational study; Stochastic intervention; Nonparametric methods; Treatment effect; Influence functions


1 Introduction

One of the central goals of statistical methods in epidemiology, social sciences and economics is to establish the main effect of an exposure $X$ on an outcome $Y$ and to determine its magnitude and direction. When the exposure is continuous (e.g. dose, duration, frequency), nonparametrically defining main effect estimands is not so straightforward. Traditional parametric regression methods define main effects through parameters indexing a model for the conditional mean outcome given exposure and a sufficient collection of confounders, $Z$, an approach which is problematic for several reasons.

The approach relies entirely on correct specification of the outcome model. However, in practice, regression models tend to be chosen for their mathematical convenience, rather than because of any a priori knowledge of the data generating mechanism. This problem persists when data adaptive variable selection methods are used to choose a working model from a set of candidate models, in which case the uncertainty in choosing the right model tends to be systematically ignored. Similar concerns apply to methods which adapt inverse probability weighting to the continuous exposure setting (Hirano and Imbens, 2005, Imai and Van Dyk, 2004, Galvao and Wang, 2015), and use models for the exposure density given confounders. Additionally, when the outcome model itself is complicated, for example when machine learning methods are used to model interaction terms and non-linearities, it may be difficult to define parsimonious scalar summary statistics, thereby encouraging researchers to ignore these complexities (Breiman, 2001).

When the exposure is binary (coded 0,1), one can draw on a rich literature of causal effects to nonparametrically define main effect estimands of interest, for example through the average treatment effect (ATE) (Robins et al., 1994), which under standard assumptions is identified by \( \tau = E\{m(1, Z) - m(0, Z)\} \), where $m(x, z) = E(Y|X = x, Z = z)$ is the conditional response surface. The ATE is motivated by contrasting the mean outcome in two counterfactual worlds, where all units are assigned the exposure levels 1 and 0 respectively (Rubin, 1974). Regular asymptotically linear estimators for the ATE (and weighted variations) may be constructed which permit valid inference even when data adaptive methods are used to fit working models (Zheng and van der Laan, 2011; Chernozhukov et al., 2018).

The dose-response curve is perhaps the most common generalization of the ATE to continuous exposures. It imagines a counterfactual world where an intervention assigns the same exposure level for all units (Robins et al., 2001; Kennedy et al., 2017). The result is a function of the intervention level, which under standard assumptions, is identified by $\varphi(x) = E\{m(x, Z)\}$. This curve, however, is usually also problematic for the following reasons.

Firstly, interventions that set the exposure to the same level are often unrealistic and therefore scientifically less interesting. This is even more so in settings where confounders are strong predictors of exposure (e.g. diet and physical activity level are strong predictors of exposure human body mass index), thus assigning the value $X = x^*$ may represent an unrealistic intervention for treatment units in some confounder subgroups, even when for others it may be reasonable. We would argue that the dose-response curve is therefore practically uninformative for answering many scientific questions of interest, not least in the exploratory stage of an analysis where there may not be a particular intervention in mind.

Secondly, in the setting of poor overlap between confounder subgroups, estimation of $\varphi(x^*)$ may also require significant extrapolation, for example to obtain an estimate of $m(x^*, z_0)$ when there are few observations of $X \approx x^*$ for a particular confounder group, $z_0$. Additional concerns relate to the fact that the dose-response curve is an infinite dimensional parameter (i.e. a function) rather than a scalar summary statistic. This inherently makes estimation more difficult and also means there is no clear way to summarize the resulting curve once it has been obtained, see e.g. (Kennedy...
et al. (2017); Neugebauer and van der Laan (2007) for estimation strategies.

In view of these concerns we make an alternative proposal, which is to imagine a counterfactual world where the exposure distribution for all treatment units is shifted by an infinitesimal amount. This proposal has the advantage that for all units we consider only realistic exposure values. It also relates to an existing literature on derivative effects (sometimes called weighted average derivatives or average partial effects), popular in econometrics (Härdle and Stoker 1989; Powell et al. 1989; Newey and Stoker 1993). These were originally motivated by semi-parametric index models, under which derivative effects are proportional to indexing parameters. In our developments we rely instead on a causal interpretation of derivative effects, which follows from the identification result,

$$\lim_{\epsilon \to 0} \epsilon^{-1} E(Y^{x+\epsilon} - Y^x | Z = z) = m'(x, z)$$

We refer to the left hand side above as the counterfactual derivative, where $Y^x$ is the potential outcome under an intervention which assigns exposure level $x$ and superscript prime denotes the derivative w.r.t. $x$, which we assume exists. One such effect estimand is the average derivative effect (ADE), $E\{m'(X, Z)\}$, which considers the effect of shifting each individual’s observed exposure and acts as a continuous analogue of the ATE. We note that the ADE is not the same as the average derivative of the dose-response curve, which we discuss in Section 3.

Inference of the ADE usually requires estimation of (a) the conditional density of exposure given confounders and (b) the derivative of (a) w.r.t. exposure, see e.g. Härdle and Stoker (1989; Newey and Stoker 1993; Cattaneo et al. 2013). Estimates of (a) and (b) are typically obtained by non-parametric kernel based methods, however, the reliance on kernel methods introduces complicated biases as the dimension of $Z$ increases, due to the curse of dimensionality (Cattaneo et al. 2013).

Alternative estimation strategies, when $Z$ is high dimensional, rely on parametric (usually single-index) models for the conditional mean outcome (Wooldridge and Zhu 2020; Hirshberg and Wager 2020). These assume that the outcome model is known and apriori specified, which is problematic for the reasons mentioned above. Instead we advocate changing the focus to weighted derivative effect estimands which are amenable to data adaptive estimation of $m(x, z)$.

In the current paper we show that two such weighted derivative effect estimands, which we call ‘contrast effects’, are given by,

$$\Lambda = E \left\{ \frac{\text{cov}(v(X), Y | Z)}{\text{cov}(v(X), X | Z)} \right\} \quad (2)$$

and

$$\bar{\Lambda} = \frac{E \{\text{cov}(v(X), Y | Z)\}}{E \{\text{cov}(v(X), X | Z)\}}, \quad (3)$$

when $X$ is continuous and $m'(x, z)$ exists, although they remain well defined even when $X$ is discrete or $m(x, z)$ is not differentiable. These effects are indexed by a known function $v(x)$. When $X$ is binary, and $v(1) \neq v(0)$ are finite, then $\Lambda$ reduces to the ATE and $\bar{\Lambda}$ to the propensity overlap weighted effect (Crump et al. 2006), which we show is an optimally efficient estimand of our class (Section 5). In the case where $v(x) = x$ then $\bar{\Lambda}$ appears in work by Vansteelandt and Dukes (2020); Robins et al. (2008); Newey and Robins (2018) with the numerator appearing in recent work on conditional independence testing (Shah and Peters 2020).

In Section 5, estimators for $\Lambda$ and $\bar{\Lambda}$ are derived which attain the efficiency bound under the nonparametric model. These estimators do not contain contributions from (a) or (b), thus alleviating the aforementioned concerns regarding estimation of the ADE.
## 2 Causal Estimands

Suppose that \((Y, X, Z)\) is distributed according to an unknown distribution \(P\). When the exposure \(X\) is binary and coded \((0,1)\), the object of inference is often defined with reference to the conditional (heterogeneous) treatment effect, \(\tau(z) = E(Y^1 - Y^0 | Z = z)\) where \(E(.)\) denotes expectation with respect to \(P\). Marginal effects are usually defined as a weighted average of this conditional effect \(\tau = E\{w(Z)\tau(Z)\}\), where \(w(Z)\) represents a ‘subgroup weight’ function which we assume is non-negative and normalized such that \(E\{w(Z)\} = 1\).

The unitary weight \(w(Z) = 1\), recovers the ATE. However, an alternative is the so-called overlap weight, \(w(Z) \propto \pi(Z)\{1 - \pi(Z)\}\) where \(\pi(z) = E(X | Z = z)\) and the constant of proportionality is fixed by normalization. This weight is advocated due to optimality results \cite{Crump2009} and due to its utility in policy learning \cite{Kallus2020}. Under standard assumptions of consistency \((X = x \implies Y = Y^x)\) and ignorability \((Y^x \perp X | Z\) for all \(x)\), one obtains the identification result,

\[
E(Y^x | Z = z) = E(Y^x | X = x, Z = z) = E(Y | X = x, Z = z) = m(x, z).
\]

Letting superscript dagger denote a binary difference operator, i.e. \(m^\dagger(z) = m(1, z) - m(0, z)\), it follows that \(\tau(z) = m^\dagger(z)\) and \(\tau = E\{w(Z)m^\dagger(Z)\}\) under these assumptions. In the binary setting, interest is in comparing exposure levels \(X = 1\) and \(X = 0\), however when \(X\) is continuous, it is less clear which levels are of interest. We propose causal estimands which compare the observed exposure level \(X\) with an infinitesimally separated exposure level, \(X + \epsilon\) in the limit where \(\epsilon \rightarrow 0\). Under the identification assumptions above, and assuming such a limit exists, one obtains the identification result for the counterfactual derivative in \([\text{1}]\). We propose taking a weighted average of the counterfactual derivative over exposure levels to obtain a conditional estimand which depends only on \(z\), and which we shall view as a continuous exposure analogue of \(\tau(z)\),

\[
\psi(z) = \lim_{\epsilon \rightarrow 0} \epsilon^{-1} \int E(Y^{x+\epsilon} - Y^x | Z = z)w(x | z)dP(x | z)
\]

Here \(w(x | z)\) represents an ‘exposure weight’ which is non-negative and normalized such that \(E\{w(X | Z) | Z\} = 1\). This exposure weight is the principal complication in moving from the binary to continuous exposure setting, since \(\psi(z)\) represents a class of estimands indexed by the exposure weight function, whereas \(\tau(z)\) is unique. As before, a marginal estimand is defined by taking a weighted average of this conditional effect, \(\Psi = E\{w(Z)\psi(Z)\}\), which is a continuous exposure analogue of \(\tau\).

Using the identification result in \([\text{1}]\), we write \(\psi(z) = E\{w(X | Z)m'(X, Z) | Z = z\}\) and the marginal estimand \(\Psi = E\{w(X, Z)m'(X, Z)\}\), where \(w(x, z) = w(x | z)w(z)\). Estimands of this type are referred to as derivative effects and were introduced for the study of semi-parametric index models. In previous treatments of derivative effects, the function \(w(x, z)\) is usually assumed to be known, but we allow for it to be an unknown function of the distribution, \(P\). See \cite{Powell1989} for a ‘density weighting’ example where weights are not known.

The idea of exposure weighing is closely related to the theory of stochastic interventions \cite{Diaz2012, Kennedy2019}. In this theory, one considers a counterfactual world where, for each unit in the population, the exposure is drawn from an alternative ‘intervention distribution’, \(\tilde{P}\), which is a probability distribution for \(X\) given \(Z\). The counterfactual mean outcome under this intervention is compared with that from the true distribution, \(P\), resulting in the binary stochastic intervention estimand,

\[
\int E(Y^{x_1} - Y^{x_0} | Z = z)d\tilde{P}(x_1 | z)dP(x_0 | z)dP(z) = \int \tau(z) \{\tilde{\pi}(z) - \pi(z)\} dP(z)
\]
where \( \pi(z) = E_{P}(X|Z = z) \). Similarly, the exposure weight describes an intervention distribution, \( d\tilde{P}(x|z) = w(x|z)dP(x|z) \), since the exposure weight is normalized and non-negative. Thus we rewrite the conditional derivative effect,

\[
\psi(z) = \lim_{\epsilon \to 0} \epsilon^{-1} \int E(Y_{x+\epsilon} - Y_{x}|Z = z)d\tilde{P}(x|z).
\]

It follows that the proposed conditional effects can be interpreted as follows. First we imagine a counterfactual world, where we intervene on the distribution of exposure given confounders, replacing the true distribution with the intervention distribution, \( \tilde{P} \). Next we imagine a second counterfactual world where the exposure is distributed according to the intervention distribution, but with an infinitesimal perturbation for all treatment units. The proposed derivative effects estimand is the difference in mean outcome between these two worlds, rescaled by the perturbation size in the sense of the derivative. We note that setting the intervention distribution to the true distribution (i.e. \( \tilde{P} = P \)) recovers the ADE.

Under consistency and ignorability we write \( \psi(z) = E_{\tilde{P}}\{m'(X,Z)|Z = z\} \), which we refer to as the ‘difference sampling form of the derivative effects estimand’ since the difference \( m'(x,z) \) is sampled according to the intervention distribution, \( \tilde{P} \). Furthermore, difference sampling representations of \( \tau \) and \( \Psi \) may also be written using the subgroup weight to define an alternative distribution of \( Z \), \( d\tilde{P}(z) = w(z)dP(z) \). Hence, \( \tau = E_{\tilde{P}}\{m'(z)\} \) and \( \Psi = E_{\tilde{P}}\{m'(X,Z)\} \).

Generalizations of \( \tau(z) \) and \( \tau \) sometimes introduce GLM link functions to define estimands on a link function scale or else could consider other functionals of the potential outcome, such as distribution quantiles. For this reason, in the sections which follow we shall refer to binary difference effects and derivative effects defined over an arbitrary (differentiable) function \( g(x,z) \), restricting to the choice \( g(x,z) = m(x,z) \) when required. The difference sampling representations of the conditional and marginal effects are given by

\[
\tau(z) = g^\dagger(z) = g(1,z) - g(0,z) \tag{4}
\]

\[
\tau = E\{w(Z)g^\dagger(Z)\} = E_{\tilde{P}}\{g^\dagger(Z)\} \tag{5}
\]

\[
\psi(z) = E\{w(X|Z)g'(X,Z)|Z = z\} = E_{\tilde{P}}\{g'(X,Z)|Z = z\} \tag{6}
\]

\[
\Psi = E\{w(X,Z)g'(X,Z)\} = E_{\tilde{P}}\{g'(X,Z)\}. \tag{7}
\]

### 3 Contrast representations

In this section we show that both binary difference and derivative effects permit an alternative representation which we call the contrast representation. This representation unifies the two classes and enables new estimands to be proposed, as discussed in Section 4.1. We begin with the observation that, when \( X \) is binary, generally \( g(x,z) = g(0,z) + \tau(z)x \). It follows that for an arbitrary function, \( l(x|z) \),

\[
E\{l(X|Z)g(X,Z)|Z\} = E\{l(X|Z)|Z\}g(0,Z) + E\{l(X|Z)X|z\}\tau(Z).
\]

We define a ‘contrast function’ as a function, \( l(x|z) \), such that that \( E\{l(X|Z)|Z\} = 0 \) and \( E\{l(X|Z)X|Z\} = 1 \). These conditions are chosen since they allow us to write a ‘contrast representation’ form of the conditional and marginal treatment effect respectively,

\[
\tau(z) = E\{l(X|Z)g(X,Z)|Z = z\} \quad \tag{8}
\]

\[
\tau = E\{w(Z)l(X,Z)g(X,Z)\}. \quad \tag{9}
\]
For the estimands where, \(g(x, z) = m(x, z)\) the contrast representation simplifies to a form where we replace \(g(X, Z)\) with \(Y\) in the expressions above. For binary exposures, the contrast function is unique (for each \(z\)) since it must satisfy two constraints and has two degrees of freedom \((x = 0\) and \(1\)). Assuming \(\text{var}(X|Z = z) \neq 0\) for all \(z\), the contrast function is

\[
l(x|z) = -\frac{x - \pi(z)}{\pi(z)\{1 - \pi(z)\}}
\]

Invoking regularity conditions, Powell et al. (1989) showed that derivative effects can be rewritten in a contrast representation form analogous to (8) and (9) (see Appendix). These conditions require that \(X\) is a continuous random variable and thus has a conditional density function, \(f(x|z)\), given \(Z = z\). Writing the intervention density, \(\tilde{f}(x|z) = w(x|z)f(x|z)\), we also require (A1) that the derivative \(\tilde{f}'(x|z)\) exists, and (A2) that \(\tilde{f}(x|z) = 0\) for \(x\) on the boundary of the support of \(X\). Under these conditions,

\[
\psi(z) = E\{l(X|Z)g(X, Z)|Z = z\}
\]

\[
\Psi = E\{w(Z)l(X|Z)g(X, Z)\}
\]

where \(l(x|z)\) is the contrast function,

\[
l(x|z) = -\frac{\tilde{f}'(x|z)}{f(x|z)} = -w'(x|z) - w(x|z)\frac{f'(x|z)}{f(x|z)}
\]

As before, for the choice \(g(x, z) = m(x, z)\) the expressions in (11) and (12) simplify to a form where \(g(X, Z)\) is replaced with \(Y\). With regard to assumption A1, we argue that it is hard to imagine a practical setting where we are willing to assume that \(g'(x, z)\) exists, but not \(f'(x|z)\), with the former required by the definition of a derivative effect.

We now apply (13) in two examples, both in the setting where \(g(x, z) = m(x, z)\). The ADE (Example 1) uses a unitary exposure weight \(w(x|z) = 1\), and hence the intervention distribution is the true distribution \(\tilde{f}(x|z) = f(x|z)\). To highlight the difference between the ADE and dose-response curve modelling, we consider that the average derivative of the dose-response curve (Example 2) is also a derivative effect (under standard causal assumptions). This estimand sets the intervention distribution to the marginal exposure distribution, \(\tilde{f}(x|z) = f(x|z)\).

**Example 1** (Average derivative effect). The derivative effect with unitary exposure and subgroup weight, i.e. \(w(X|Z) = w(Z) = 1\) was originally proposed by Härdle and Stoker (1989). This results in the conditional and marginal derivative effects, \(E\{m'(X, Z)|Z = z\}\), with marginal effect \(E\{m'(X, Z)\}\). This estimand has the contrast function,

\[
l(x|z) = -\frac{f'(x|z)}{f(x|z)} = -\frac{d\log f(x|z)}{dx}
\]

**Example 2** (Average dose-response derivative). Consider the dose-response curve \(\varphi(x) = E\{m(x, Z)\}\). The mean derivative of this curve, \(E\{\varphi'(x)\}\) is a derivative effect with exposure weight \(w(X|Z) = f(X)/f(X|Z)\), and subgroup weight \(w(Z) = 1\), where \(f(x)\) is the marginal exposure density, and we make a positivity assumption such that \(f(x) \neq 0 \implies f(x|z) \neq 0\) for all \(x\). This estimand has the contrast function,

\[
l(x|z) = -\frac{f'(x)}{f(x|z)}
\]
A key contribution of the current paper is an inversion of the result in (13), providing an expression for the intervention distribution associated with certain contrast functions. The implication of this Theorem is a duality between the contrast function and the intervention distribution, allowing new derivative effect estimands to be specified through their contrast rather than difference sampling representations. Such estimands also reduce to the binary difference sampling form in [5], when $X$ is binary.

**Theorem 1.** Let $l(x|z)$ be a contrast function and let $F(x|z)$ be the distribution of $X$ given $Z = z$. If, for all $x$,

$$
\tilde{f}(x|z) = -E\{l(X|Z)|X \leq x, Z = z\}F(x|z) \geq 0
$$

then $\tilde{f}(x|z)$ is probability density function. Furthermore, if $X$ is a continuous random variable, then, for all differentiable functions $g(x, z)$,

$$
E\{l(X|Z)g(X, Z)|Z = z\} = E_{\tilde{f}}\{g'(X, Z)|Z = z\}
$$

Proof in Appendix.

The inequality in (15) is not generally satisfied by an arbitrary contrast function, however Lemma 1.1 below guarantees that this inequality is satisfied when the contrast function is constructed from a monotonic function. Observe that by centering and scaling some function, $v(x, z)$, one may construct the contrast function,

$$
l(x|z) = \frac{v(x, z) - E\{v(X, Z)|Z = z\}}{\text{cov}\{v(X, Z), X|Z = z\}}
$$

provided that $\text{cov}\{v(X, Z), X|Z = z\} \neq 0$ for all $z$. The conditional estimand associated with this contrast function is,

$$
\psi(z) = \frac{\text{cov}\{v(X, Z), g(X, Z)|Z = z\}}{\text{cov}\{v(X, Z), X|Z = z\}}.
$$

In Section 4.1 we propose estimands of this type for which $v(x, z) = v(x)$ is a known function.

**Lemma 1.1 (Sufficiency Condition for Theorem 1).** Let $v(x, z)$ be a function which is monotonically increasing or decreasing (but not constant) in $x$, for $x$ on the support of $X$. Then the contrast function in (17) implies a valid density function, $\tilde{f}(x|z)$ defined in (15). Proof in Appendix.

## 4 Contrast Effects

### 4.1 Constructing new estimands

Here we define main effect estimands by their contrast representations, with the understanding that a difference sampling representation may be obtained under conditions described in Theorem 1. This approach naturally leads to a broad class of estimands, which we call contrast effects. Contrast effects have the advantage that they remain well-defined even when $g(x, z)$ is not differentiable, or the exposure is not continuous - except of course when the contrast function itself is not defined for non-continuous exposures, as in Examples 1 and 2.

At this point we seek inspiration from the contrast function of the ADE (14) to derive new contrast functions and thus specify new contrast effects. Specifically we consider the form of (14)
when \( X \) follows a known parametric distribution conditional on \( Z = z \). Consider the normal, gamma \((X > 0)\) and asymmetric Laplace distributions (Yu and Zhang, 2005) with the respective density functions

\[
\begin{align*}
f_1(x|\mu, \sigma) &= \frac{1}{\sqrt{2\pi\sigma}} \exp \left\{ -\frac{(x - \mu)^2}{2\sigma^2} \right\} \\
f_2(x|\alpha, \beta) &= \frac{\beta}{\Gamma(\alpha)} x^{\alpha - 1} \exp(-\beta x) \\
f_3(x|p, \sigma, x_0) &= \frac{p(1-p)}{\sigma} \exp \left[ -\frac{(x - x_0)}{\sigma} \left\{ \theta(x - x_0) - p \right\} \right]
\end{align*}
\]

where \( x_0 \) is a known value and the parameters \( \mu, \sigma > 0, \alpha > 0, \beta > 0, p \in (0, 1) \) are all constant given \( Z = z \). Also, \( \Gamma(.) \) represents the gamma function and \( \theta(u) \) is a step function which takes the value 1 when \( u > 0 \) and 0 otherwise. Plugging these density functions, in turn, into (14) gives the contrast functions

\[
\begin{align*}
-\frac{d \log f_1(x|\mu, \sigma^2)}{dx} &= \frac{x - \mu}{\sigma^2} \\
-\frac{d \log f_2(x|\alpha, \beta)}{dx} &= (1 - \alpha)x^{-1} + \beta \\
-\frac{d \log f_3(x|\mu, \sigma^2)}{dx} &= \frac{\theta(x - x_0) - p}{\sigma} \quad .
\end{align*}
\]

Technically the third equation above describes the derivative for \( x \neq x_0 \), since \( f_3(x|p, \sigma, x_0) \) is not differentiable at this point. This is not problematic, however, since these expressions are used only to inspire well defined contrast effects. It is readily seen that all three contrast functions share the property that they are of the form of a known function, \( v(x) \), up to centring and scaling by parameters which are constant given \( z \). These \( v(x) \) functions are \( x, x^{-1} \) and \( \theta(x - x_0) \) respectively.

We note that most common distributions do not share this property and will result in more complicated contrast functions. For instance, in the third example above, we were only able to ensure this property by letting \( x_0 \) be a constant which was known a priori. Inspired by these distributions, we propose setting \( v(x, z) = v(x) \) in (18) to define three new conditional contrast effect estimands, with marginal effects given by \( \Psi = E\{w(Z)|\psi(Z)\} \) as before. These are given in Examples 3 to 5. Later in this section we will clarify how these estimands relate to (weighted) ADEs.

**Example 3 (Average Least Squares Effects).** This is an example of the construction in (18), where \( v(x, z) = x \) and one obtains the contrast function, and conditional estimands,

\[
\begin{align*}
l(x|z) &= \frac{x - E(X|Z = z)}{\var(X|Z = z)} \\
\psi(z) &= \frac{\text{cov}(X, g(X, Z)|Z = z)}{\var(X|Z = z)}
\end{align*}
\]

with the marginal estimand \( \Psi = E\{w(Z)|\psi(Z)\} \). When \( X \) is binary, then this contrast function recovers the binary contrast function in (10). We refer to these estimands as weighted Average Least Squares Effects (ALSE) due to their connection with the least squares problem.

\[
\begin{align*}
\psi(\cdot) &= \arg \min_{\psi(\cdot) \in \mathcal{F}} E \left( [g(X, Z) - g(Z) - \psi(Z)\{X - \pi(Z)\}]^2 \right) \\
\frac{E\{\text{cov}(X, g(X, Z)|Z)\}}{E\{\var(X|Z)\}} &= \arg \min_{\psi \in \mathbb{R}} E \left( [g(X, Z) - g(Z) - \psi\{X - \pi(Z)\}]^2 \right)
\end{align*}
\]
where \( g(z) = E\{g(X,Z)|Z = z\} \) and \( \mathcal{F} \) is the set of set of all functions which map confounder vectors to the real numbers, see e.g. Chambaz et al. (2012) for a similar proposal. The second expression above is the ‘variance weighted ALSE’, which is an average over the conditional ALSE, \( \psi(z) \), with variance subgroup weight \( w(Z) \propto \text{var}(X|Z) \). ALSEs are also proposed by Vansteelandt and Dukes (2020) in the case where \( g(x, z) = h(m(x, z)) \) and \( h(.) \) is a canonical GLM link function. When \( h(.) \) is the identity link, the unitary weighted ALSE (i.e. \( w(Z) = 1 \)), appears in Hirshberg and Wager (2020). The variance weighted ALSE appears in Robins et al. (2008); Newey and Robins (2018). Vansteelandt and Dukes (2020) advocate for variance weights on the basis that, for the identity link, the variance weighted ALSE reduces to the propensity overlap weighted effect when the exposure is binary. We derive a similar optimality result in Section 5.

**Example 4** (Gamma distribution based). Consider the construction in (18), where \( v(x, z) = x^{-1} \) and one obtains the contrast function, and marginal estimands,

\[
\psi = E\left\{ w(Z) \frac{\text{cov}(X^{-1}, g(X, Z)|Z)}{\text{cov}(X^{-1}, X|Z)} \right\}
\]

where we note that \( \text{cov}(X^{-1}, X|Z) = 1 - \pi(Z)E(X^{-1}|Z) \). The fact that \( X^{-1} \) appears in this estimand is problematic when the support of \( X \) contains 0 or negative values. Estimands of this type, however, might be useful for quantifying the effect of exposure on outcome when the exposure is known to be positive and skewed. Such exposures could include length of hospital stay in biostatistical problems or level of household income in econometric settings.

Traditionally, when presented with non-normality of a regressor, \( X \), one might consider using a linear model for outcome, \( Y \), with the reciprocal transformed regressor, \( X^{-1} \), as a predictor, so long as one is not interested in reporting effects in the original (untransformed) scale (Pek et al., 2017). The resulting main effect is parametrically defined with reference to convenient working models, which themselves raise misspecification concerns. Instead we advocate the estimand above, with \( g(x, z) = m(x, z) \), returning a nonparametric estimand (on the untransformed scale), thus alleviating misspecification concerns. Both approaches, however, are not invariant to translational shifts on the exposure scale, for example, if the exposure of interest is a temperature variable in an environmental statistics problem, then different results would be obtained by using temperature on the Celsius, Fahrenheit and Kelvin scales.

**Example 5** (Dichotomized exposure). This example is of the type constructed in (18), with \( v(x, z) = \theta(x - x_0) \), where \( x_0 \) is a known, predetermined exposure level. Denoting the survival function by \( S_0(z) = P(X > x_0|Z = z) \) then by the law of total expectation, the contrast function and conditional effect estimands can be written,

\[
\psi(z) = \frac{\theta(x - x_0) - S_0(z)}{S_0(z)\{1 - S_0(z)\}} \{ E\{X|X > x_0, Z = z\} - E\{X|X \leq x_0, Z = z\} \}
\]

with marginal estimand \( \Psi = E\{ w(Z)\psi(Z) \} \). For a binary exposure with \( x_0 \in (0,1) \) this contrast function recovers the binary contrast function in (10). The conditional effect estimand is closely related to the idea of dichotomizing a continuous exposure, i.e. treating it as a binary variable \( \theta(X - x_0) \). This is perhaps more clear in the setting \( g(x, z) = m(x, z) \) and choosing \( w(Z) \propto \text{cov}(X^{-1}, X|Z) \)
\[ E\{X|X > x_0, Z\} - E\{X|X \leq x_0, Z\} \] in which case
\[
\Psi = \frac{E\{E[Y|X > x_0, Z]\} - E\{Y|X \leq x_0, Z\}}{E\{E[X|X > x_0, Z]\} - E\{X|X \leq x_0, Z\}}
\]
which is the average treatment effect of \( \theta(X - x_0) \) on \( Y \) up to scaling by the denominator above. Selecting a normalized subgroup weight, \( w(z) \), proportional to the denominator of \( \psi \), then one obtains the propensity overlap weighted average treatment effect from a dichotomized exposure, up to a constant of proportionality,
\[
\Psi = \frac{E\{S_0(Z)\{1 - S_0(Z)\}\{E[Y|X > x_0, Z]\} - E\{E[Y|X \leq x_0, Z]\}}{E\{S_0(Z)\{1 - S_0(Z)\}\{E[X|X > x_0, Z]\} - E\{X|X \leq x_0, Z]\}}
\]

Dichotomization of a continuous exposure is used routinely in psychology and epidemiology, with its use in regression analysis usually criticized for unnecessarily introducing variable censoring (MacCallum et al., 2002; Royston et al., 2006). The dichotomized exposure estimands described above, however, may be useful summary statistics for the effect of exposure on outcome, in certain settings. For example, for the subgroup weight \( w(Z) = 1 \), \( \Psi \) reduces to the ADE when exposure follows an asymmetric Laplace distribution given confounders, with centrality parameter, \( x_0 \), i.e. \( X \) is exponentially distributed either side of \( x_0 \). Such exposures could include, for example, duration from surgery to follow up in biostatistical problems, when existing hospital policy assigns a specific value (e.g. \( x_0 = 14 \) days), but some variation in this exposure is observed (e.g. due to patient/doctor availability or appointment cancellations).

Finally we arrive at the main effect estimands which we advocate in the current paper and are given by \( \Lambda \) and \( \bar{\Lambda} \), as in \([2] \) and \([9] \). Both are contrast effects of the form of \( E\{w(Z)\lambda(Z)\} \) where \( \lambda(z) \) is the conditional contrast effect obtained by setting \( v(x, z) = v(x) \) and \( g(x, z) = m(x, z) \) in \([18] \).
\[
\lambda(z) = \frac{\text{cov}\{v(X), Y|Z = z\}}{\text{cov}\{v(X), X|Z = z\}}
\]
We propose the subgroup weights \( w(Z) = 1 \) and \( w(Z) \propto \text{cov}\{v(X), X|Z\} \), resulting in \( \Lambda \) and \( \bar{\Lambda} \) respectively. For the latter subgroup weight, non-negativity is guaranteed when \( v(x) \) is monotonically increasing or decreasing (but not constant) in \( x \), which happens to be the condition stated in Lemma \([11] \). This condition is satisfied by the choices \( v(x) = x, \theta(x - x_0) \) and also \( v(x) = x^{-1} \) provided that \( x > 0 \) (or \( x < 0 \)).

The appeal of these contrast effect estimands is that \( \Lambda \) and \( \bar{\Lambda} \) are generally easier to infer than the ADE, however, in certain settings they coincide with the ADE, provided that \( m(x, z) \) is differentiable and the exposure is continuous. For instance, if the exposure is gamma distributed (conditional on \( Z \)), then for the choice \( v(x) = x^{-1} \), our estimand, \( \Lambda \), coincides with the ADE, since the contrast function in \([20] \) coincides with that of the ADE in \([14] \). Even when the exposure is not gamma distributed, however, our estimand remains interpretable, since \( \Lambda = E\hat{\rho}\{m'(X, Z)\} \) where \( \hat{\rho} \) is an intervention distribution that is derived from the true distribution according to \([13] \). In Section \([4.2] \) we describe the intervention distribution in some detail for the choice \( v(x) = x \).

The form of the subgroup weight function for \( \bar{\Lambda} \) is motivated by connections to the propensity overlap weighted average treatment effect. In fact for binary exposures, \( \bar{\Lambda} \) reduces to the propensity overlap weighted ATE and \( \Lambda \) to the ATE itself, provided that \( v(1) \) and \( v(0) \) are not equal and are finite, which is true for \( v(x) = x, \theta(x - x_0) \) provided that \( x_0 \in (0, 1) \), but is not true for \( v(x) = x^{-1} \) unless we recode our binary exposure (e.g. \( v(-1) \neq v(1) \)).
The interpretation of weighted ALSEs as derivative effect is a novel contribution of this work, however, relates closely to three other observations in the literature. The first, by Banerjee (2007), is that an estimator of the ADE (Example 1) may be constructed by partitioning the support of $X$ into disjoint bins, and applying a least squares regression to each bin. The estimate is given by the average variance weighted ALSE across bins, weighted by the number of observations in each bin. The second observation, by Buja et al. (2019) is that the ordinary least squares (OLS) coefficient may be interpreted as a weighted sum of ‘slopes’ between pairs of observations, without invoking differentiability. They advocate for interpreting the OLS coefficient as a projection of $m(x, z)$ on to a linear model. The third observation, by Hirshberg and Wager (2020), is that when the function of interest is, in truth, conditionally linear, then the unitary weighted ALSE recovers the ADE. The key difference between Hirshberg and Wager (2020) and the current work is that our interpretation does not rely on any functional form for $m(x, z)$ beyond differentiability. Rather, we interpret the unitary weighted ALSE as a derivative effect with a certain kind of exposure weighting.

4.2 ALSE intervention distribution

Here we examine the intervention distribution associated with the ALSE, i.e. the distribution obtained from (15) with the contrast function in (19). Using the total law of expectation, the density of the ALSE intervention distribution is,

$$
\hat{f}(x) = \frac{F(x|z)\{1 - F(x|z)\}}{\text{var}(X|Z = z)} \{E(X|X > x, Z = z) - E(X|X \leq x, Z = z)\}
$$

(23)

It is informative to consider the cumulant function of this distribution, $\hat{K}(t|z) = \log E_{\hat{f}}(e^{tx}|Z = z)$. The cumulant function of this distribution, in terms of the cumulant function of the true distribution, $K(t|z) = \log E(e^{tx}|Z = z)$, and its derivative, $K'(t|z)$ is

$$
\hat{K}(t|z) = K(t|z) + \log \left( \frac{K'(t|z) - \kappa_1}{t\kappa_2} \right)
$$

(24)

where $\kappa_n = \kappa_n(z)$ is the $n$th cumulant of the true exposure distribution given $Z = z$ (see Appendix for details). The ALSE intervention distribution is therefore that of a shifted exposure, $\hat{X} = X + \delta$, where $\delta$ is a random variable, which is conditionally independent of $X$ given $Z$, with cumulant function given by the second term on the right hand side of (24). Setting this second term equal to zero and using the boundary condition that $K(0) = 0$ gives,

$$
K(t|z) = \kappa_1 t + \frac{\kappa_2 t^2}{2}
$$

This is exactly the cumulant function of a normally distributed variable, with mean $\kappa_1$ and variance $\kappa_2$. Thus, if $X$ is normally distributed (conditional on $Z$), then the ALSE intervention distribution is the true distribution, and this is the only exposure distribution for which this is the case.

To consider other exposure distributions, we imagine a transformation, $\mathcal{F}$, which transforms a probability density $f(x|z)$ to its associated ALSE intervention distribution, $\hat{f}(x|z)$, according to (23), i.e. $\mathcal{F}\{f(.)|z\}(x) = \hat{f}(x|z)$. This transformation preserves the symmetry of the density function, as formalized in Theorem 2. We apply this transformation to some well-known distributions to obtain the results in Table 1. Illustrative plots of which are shown in Fig. 1.

**Theorem 2.** Let $f(x)$ be a distribution, with finite mean $\mu$, and finite variance.

$$
f(\mu + x) = f(\mu - x) \implies \mathcal{F}\{f(.)\}(\mu + x) = \mathcal{F}\{f(.)\}(\mu - x)
$$

Proof in Appendix.
Table 1: ALSE intervention distribution associated with common distributions. For each result, \( f(x|.) \) denotes the density function of the given distribution. See Appendix for details.

| Distribution | Parameters | Result |
|--------------|------------|--------|
| Normal       | mean \( \mu \), variance \( \sigma^2 \) | \( F\{ f(\mu, \sigma) \}(x) = f(x|\mu, \sigma) \) |
| Gamma        | shape \( \alpha \), rate \( \beta \) | \( F\{ f(\alpha, \beta) \}(x) = f(x|\alpha + 1, \beta) \) |
| Chi-Squared  | degrees of freedom \( k \) | \( F\{ f(k) \}(x) = f(x|k + 2) \) |
| Beta         | shape \( \alpha \) and \( \beta \) | \( F\{ f(\alpha, \beta) \}(x) = f(x|\alpha + 1, \beta + 1) \) |
| Beta Prime   | shape \( \alpha \) and \( \beta > 2 \) | \( F\{ f(\alpha, \beta) \}(x) = f(x|\alpha + 1, \beta - 2) \) |

Figure 1: Density functions of the ALSE intervention distribution (red) corresponding to various true exposure distributions (blue) with the median of the true distribution marked with a dashed line. For the top row of plots, the exposure is in truth gamma distributed with \( \beta = 1 \) and \( \alpha = 1, 2, 5, 5 \). For the second row, the exposure is in truth beta distributed with \( (\alpha, \beta) = (1, 1), (2, 3), (1, 2) \). For the third row the exposure is beta prime distributed with \( (\alpha, \beta) = (1, 3), (2, 5), (2, 3) \).
5 Efficiency Results

For our discussion of efficiency and estimation we restrict ourselves to the case where $g(x,z) = m(x,z)$ is the conditional response function. We also draw heavily on nonparametric inference methods using influence curves (ICs), and recommend two recent tutorial papers for an introduction to these ideas [Hines et al., 2021; Fisher and Kennedy, 2020]. In the nonparametric setting, an IC is a model-free, mean zero, functional of the true data distribution, which characterizes the sensitivity of an estimand to small changes in the data distribution. As such, ICs are useful for constructing efficient estimators and for understanding the asymptotic efficiency bounds of these efficient estimators. This efficiency bound, however, is a property of the estimand itself and is given by the variance of the IC, which is assumed to be finite.

In their work on overlap treatment effect estimands, Crump et al. (2006) consider the efficiency bound of the weighted ATE, $	au = E\{w(Z)m'(Z)\}$, for a binary exposure, where $w(z)$ is a known normalized weight. For this estimand, the IC of a single observation, $o_i = (y_i, x_i, z_i)$, is,

$$
\phi_\tau(o_i) = w(z_i)l(x_i|z_i)\{y_i - m(x_i, z_i)\} + w(z_i)m'(z_i) - \tau
$$

(25)

where $l(x|z)$ is the binary contrast function in (10). In the continuous exposure setting, we derive analogous results for the derivative effect, $\Psi = E\{w(X,Z)m'(X,Z)\}$. According to Newey and Stoker (1993), when the weight function, $w(x,z) = w(x|z)w(z)$, is known and A1 and A2 (Section 3) are assumed, the IC of $\Psi$ is

$$
\phi_\Psi(o_i) = w(z_i)l(x_i|z_i)\{y_i - m(x_i, z_i)\} + w(z_i)w(x_i|z_i)m'(x_i, z_i) - \Psi
$$

(26)

where $l(x|z)$ is the contrast function in (13). For the contrast effects proposed in the current paper, the exposure weight function is unknown, however, the IC above, where the weight is known, offers some insight into efficiency optimization. In analogy with Crump et al. (2006) we minimize the efficiency bound of an efficient estimator, $\hat{\Psi}$, of the sample analogue of $\Psi$, based on a sample of $n$, iid observations,

$$
\Psi_S = n^{-1}\sum_{i=1}^{n} w(z_i)w(x_i|z_i)m'(x_i, z_i)
$$

$$
n^{1/2}(\hat{\Psi} - \Psi_S) \xrightarrow{d} \mathcal{N}(0, V)
$$

$$
V = E\{w^2(Z)^2(X|Z)\sigma^2(X, Z)\}
$$

where $\sigma^2(x,z) = \text{var}(Y|X=x, Z=z)$. The efficiency bound with respect to $\Psi_S$, rather than $\Psi$, is chosen so that the final two terms in (26) may be disregarded. These terms capture the difference between the ADE conditional on the sample distribution and that of the population as a whole. The principal extension in moving from the binary to continuous exposure setting is that the contrast function is no longer unique, and must also be optimized. Fortunately, Theorem L offers constraints on the contrast function under which a derivative effect is obtained. We therefore minimize $V$ subject to $E\{l(X|Z)|Z\} = 0$, $E\{l(X|Z)X|Z\} = 1$, and $E\{w(Z)\} = 1$.

The optimal solution is given in general by Theorem 3. When $Y$ is homoscedastic, i.e. $\sigma^2(x,z)$ is constant, this optimal solution recovers the variance weighted estimand $\bar{\Lambda}$ with $v(x) = x$. The variance subgroup weight was previously motivated by Vansteelandt and Dukes (2020) because it reduces to the propensity overlap weighted effect when the exposure is binary, however, this is unsurprising because the latter minimizes a similar efficiency bound.
Theorem 3 (Optimally weighted derivative effect). Minimizing $V$ subject to the constraints, $E\{l(X|Z)|Z\} = 0$, $E\{l(X|Z)X|Z\} = 1$, and $E\{w(Z)\} = 1$, has the solution

$$l(x|z) = \frac{a_1 - a_0 x}{(a_1^2 - a_0 a_2)\sigma^2(x, z)}$$

$$w(z) = E\left(\frac{(a_1^2 - a_0 a_2)^2}{a_1^4 - 2 a_0 a_1 b_1 + a_0^2 b_2}\right)^{-1} \frac{(a_1^2 - a_0 a_2)^2}{a_1^4 - 2 a_0 a_1 b_1 + a_0^2 b_2}$$

where $a_n = a_n(z) = E\{X^n\sigma^{-2}(X, Z)|Z = z\}$ and $b_n = b_n(z) = E\{X^n|Z = z\}$. Proof in Appendix.

Corollary 3.1 (Optimally weighted derivative effect under conditional homoscedasticity). When $Y$ is homoscedastic conditional on $z$, i.e. $\sigma^2(x, z) = \sigma^2(z)$, then the estimand implied by the contrast function and exposure weight in Theorem 3 is

$$\Psi = \frac{E\{\text{cov}(X, Y|Z)/\sigma^2(Z)\}}{E\{\text{var}(X|Z)/\sigma^2(Z)\}}$$

For proof, observe that under conditional homoscedasticity, $a_n = b_n\sigma^{-2}(z)$. Furthermore, when $Y$ is homoscedastic, i.e. $\sigma^2(x, z)$ is constant, then this optimal estimand recovers $\Lambda$ with $v(x) = x$.

In practice, a main effect estimate may be used to refute the hypothesis that $X \perp Y|Z$. This hypothesis is hard to test, since any valid test has no power against any alternative (Shah and Peters, 2020). Under the null, one is in the setting of Corollary 3.1 with $\Psi = 0$. There is no reason, however, to prefer a test based on the main effect of $X$ on $Y$ rather than the main effect of $Y$ on $X$. The ‘Generalized Covariance Measure’ proposed by Shah and Peters (2020) uses $E\{\text{cov}(X, Y|Z)\}$ as a proxy to test for independence. This is also the optimal solution we propose when $\sigma^2(x, z)$ is constant and is invariant to swapping $X$ and $Y$. The hardness of conditional independence testing arises as it is possible that $X$ and $Y$ are not independent, but $E\{\text{cov}(X, Y|Z)\} = 0$. These tests therefore have no power to test against these alternatives.

For comparison with the ICs in (25) and (26) we state the ICs of the proposed contrast effect estimands, $\Lambda$ and $\bar{\Lambda}$, as in (2) and (3). Both estimands are of the form of $E\{w(Z)\lambda(Z)\}$ with $\lambda(z)$ defined by (22) and $v(x)$ is a known function. Both also share the same contrast function,

$$l(x|z) = \frac{v(x) - E\{v(X)|Z = z\}}{\text{cov}\{v(X), X|Z = z\}}$$

but differ in their choice of subgroup weight. When the subgroup weight $w(z)$ is known, we derive the IC,

$$\phi_{\Lambda}(o_i) = w(z_i)l(x_i|z_i)\{y_i - \bar{m}(x_i, z_i)\} + w(z_i)\lambda(z_i) - \Lambda$$

where $\bar{m}(x, z) = m(z) + \lambda(z)\{x - \pi(z)\}$ and $m(z) = E\{Y|Z = z\}$. The IC of $\Lambda$ follows from the case where $w(z) = 1$. The second class of estimands, $\bar{\Lambda}$, uses the subgroup weight $w(z) \propto \text{cov}\{v(X), X|Z = z\}$ and have IC,

$$\phi_{\bar{\Lambda}}(o_i) = w(z_i)l(x_i|z_i)\{y_i - \bar{m}(x_i, z_i)\}$$

where $\bar{m}(x, z) = m(z) + \bar{\Lambda}\{x - \pi(z)\}$. These ICs closely resemble those in (25) and (26). Another reason for considering these ICs is that they may be used to construct efficient estimating equation
estimators of \( \Lambda \) and \( \tilde{\Lambda} \). By setting the sample mean IC to zero, one obtains the closed-form estimators,

\[
\hat{\Lambda} = n^{-1} \sum_{i=1}^{n} \frac{\{v(x_i) - \hat{\rho}(z_i)\}}{\hat{\beta}(z_i)} [y_i - \hat{m}(z_i) - \hat{\lambda}(z_i)\{x_i - \hat{\pi}(z_i)\}] + \hat{\lambda}(z_i)
\]

\[
\hat{\Lambda} = \sum_{i=1}^{n} \frac{\{v(x_i) - \hat{\rho}(z_i)\} y_i - \hat{m}(z_i)}{\sum_{i=1}^{n} \{v(x_i) - \hat{\rho}(z_i)\} x_i - \hat{\pi}(z_i)}.
\]

where \( \rho(z) = \mathbb{E}\{v(X)|Z = z\} \) and \( \beta(z) = \text{cov}\{v(X), X|Z = z\} \) and superscript hat denotes fitted models obtained from an independent sample. The \( \hat{\Lambda} \) estimator requires modelling the functions \( \beta(.) \) and \( \lambda(.) \), whereas the \( \hat{\Lambda} \) estimator does not, making the latter generally more straightforward. In practice, a cross-fitting approach may be used to obtain the fitted models and estimate the estimands of interest from a single sample (Chernozhukov et al., 2018). In a subsequent paper we study such estimators in greater detail.

6 Illustration

To develop intuition for the proposed estimands, we calculate the true estimand values obtained in various settings, and illustrate the estimands visually. We consider three non-linear, differentiable conditional response functions, \( m(x, z) \), under two true continuous exposure distributions, in the presence of a single standard normal confounding variable \( Z \). The two continuous exposures are,

\[
X_1 = \mathcal{N}(4 + 0.2(Z + Z^2), 1)
\]

\[
X_2 = \text{Gamma}(5, 2.5(1 + Z^2))
\]

where \( \mathcal{N}(\mu, \sigma^2) \) denotes the normal distribution with mean \( \mu \) and variance \( \sigma^2 \) and \( \text{Gamma}(\alpha, \beta) \) denotes a Gamma distribution with shape \( \alpha \) and rate \( \beta \). For each exposure, three outcomes will be considered: two continuous and one binary. These are given by replacing \( X \) with \( X_1 \) or \( X_2 \) in the following expressions

\[
Y_1 = \text{Bernoulli}(\expit(X - 2.5))
\]

\[
Y_2 = X - 2(X - 2.5)(X - 3) \exp \left( -\frac{1}{2}(X - 3)^2 \right) + \mathcal{N}(0, 1)
\]

\[
Y_3 = X - 2(X - 2.5)(X - 3) \exp \left( -\frac{1}{2}(X - 3)^2 \right) + 0.2X\theta(Z - 1) + \mathcal{N}(0, 1)
\]

The estimands of interest are those with \( v(x) = x, x^{-1} \) and \( \theta(x - 3) \) which we denote by subscript 1, 2, 3 respectively, with either a unitary subgroup weighting (i.e. \( \Lambda \)) or a variance subgroup weighting (i.e. \( \tilde{\Lambda} \)). A table of true effect estimands (obtained by Monte Carlo integration) for each exposures-outcome pair is given in Table 2 which also includes the ADE, \( \Psi = \mathbb{E}\{m'(X, Z)\} \). For outcome 1, the derivative of the conditional response function lies between 0 (when \( |X - 2.5| \) is large) and 0.25 (when \( X = 2.5 \)). For outcome 2, when \( |X - 3| \) is large then \( Y_2 \cong X \) which has derivative 1. Outcome 3 has the same conditional response function as outcome 2, however the derivative w.r.t. \( x \) is greater by 0.2 in the \( Z > 1 \) confounder subgroup. This gives some intuition as to the values one might expect to see in Table 2.

For the first and second outcomes, the conditional response function \( m(x, z) \) does not depend on \( z \) which makes these useful examples for constructing illustrative plots, for outcome 3 we consider
Figure 2: Illustration of derivative effects for six outcome (y-axis), exposure pairs (x-axis). The rows of plots represent the outcomes $Y_1$, $Y_2$ and $Y_3$ respectively. The first column of plots represents the exposure $X_1$ and the second column, $X_2$. For each plot, the grey vertical band indicates the region between the 0.1 and 0.9 quantiles, of $X$ with the vertical black line representing the median of $X$. For outcomes $Y_1$ and $Y_2$, the red line represents $E(Y|X, Z)$, for outcome $Y_3$ the red line represents $E(Y|X, Z \leq 1)$ and the orange line represents $E(Y|X, Z > 1)$. Derivative effects are given by the gradients of the plotted straight lines. The solid blue line is the average derivative effect. Green lines represent the proposed variance weighted effects and purple lines are the proposed unitary weighted effects. The dashed lines represent the choice $v(x) = x$. The dotted lines represent $v(x) = x^{-1}$ and the two-dashed line represents $v(x) = \theta(x - 3)$.

the dependence on $m(x, z)$ depends on $z$ only through the step function $\theta(z - 1)$, hence we consider this conditional response function in the settings where $z > 1$ or $z \leq 1$.

Illustrative plots for each exposure-outcome pair are provided in Figure 2. These show the true outcome conditional response function compared with various linear approximations of the response function, each of which has a gradient given by the true values of the proposed estimands when the exposure is distributed as $X_1$ and $X_2$ respectively.

These plots show that, for the same conditional response function, the two exposure distributions give different sets of true estimand values. This difference arises since for each exposure distribution and estimand the derivative of the conditional response function is assigned a different weight in different regions. To illustrate this point, the region between the 0.1 and 0.9 quantiles of the true marginal exposure distribution is marked with a grey band, with the median also marked.
Table 2: True estimand values. Subscript 1,2,3 refers to the estimands where $v(x) = x, x^{-1}$ and $\theta(x-3)$ respectively.

| Outcome | Exposure | $\Psi$ | $\Lambda_1$ | $\Lambda_2$ | $\Lambda_3$ | $\bar{\Lambda}_1$ | $\bar{\Lambda}_2$ | $\bar{\Lambda}_3$ |
|---------|----------|--------|-------------|-------------|-------------|------------------|------------------|------------------|
| 1       | 1        | 0.14   | 0.14        | 0.15        | 0.18        | 0.14             | 0.16             | 0.18             |
| 1       | 2        | 0.17   | 0.18        | 0.17        | 0.21        | 0.20             | 0.17             | 0.22             |
| 2       | 1        | 0.85   | 0.85        | 0.75        | 0.40        | 0.85             | 0.72             | 0.38             |
| 2       | 2        | 0.80   | 0.88        | 0.80        | 0.90        | 1.05             | 0.80             | 0.89             |
| 3       | 1        | 0.88   | 0.88        | 0.74        | 0.40        | 0.88             | 0.78             | 0.44             |
| 3       | 2        | 0.83   | 1.06        | 0.83        | 0.89        | 0.91             | 0.83             | 1.02             |

7 Discussion

The current work makes several contributions both to the causal inference literature and to literature regarding classical derivative effects. With regard to causal inference, we outline a causal interpretation of weighted derivative effects. We connect derivative effect estimands to the change in mean outcome under small perturbations in a stochastic exposure intervention. The appeal of these estimands is that they focus attention towards modest shifts in exposure around realistic values for each treatment unit. This is advantageous in settings where confounders are strong predictors of exposure, thus the dose-response curve may be both uninformative in answering scientific questions of interest, and too ambitious to estimate due to extrapolation concerns. Derivative effects, however, capture the magnitude and direction of the main effect, which is especially useful in an exploratory analysis, where no specific intervention is planned. They moreover provide a generic effect measure that can be used without needing to choose between many possible shift interventions that could be considered.

We extend classical results from the derivative effects in several directions. First we propose a class of contrast effect estimands which unify derivative effects and binary difference effects. Under regularity conditions, the proposed contrast effects reduce to binary difference and derivative effects when the exposure is binary and continuous respectively. We propose new contrast effects and connect these to specific stochastic intervention distributions through Theorem 1. For the ALSE estimand we describe this intervention distribution in detail. The proposed contrast effects also remain well-defined when the exposure is not continuous or binary or the response surface is not differentiable.

Secondly, we rederive weighted ALSEs, previously studied in other work, as an optimally efficient derivative effect when the outcome is homoscedastic. This is done by extending the approach by [Crump et al. (2006)] based on IC methods. We further state the ICs of the proposed estimands and derive efficient one-step estimators, which generalize the AIPW and Partialling out estimators.

Through the difference sampling representation, we see that the estimands we propose take true values which depend on the conditional response function and the conditional distribution of exposure given confounders. This was demonstrated in the illustration in Section 5 where the same conditional response functions produced different true estimand values for the exposure variables $X_1$ and $X_2$. By comparison, traditional model based regression estimands are defined by parameters indexing a model for $m(x,z)$, appears to have no dependence on the exposure distribution, however, this is only the case because the models are assumed to be true. Likewise, the dose-response curve also does not depend on the distribution of exposure given confounders, whereas the average effect of shift interventions do have such a dependence.
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A Supplementary Materials

Derivation of (13)

When (A1), \( \tilde{f}(x|z) = w(x|z)f(x|z) \) is differentiable, integration by parts gives,

\[
\Psi(z) = \int_a^b g'(x, z)\tilde{f}(x|z)dx = g(a, z)\tilde{f}(a|z) - g(b, z)\tilde{f}(b|z) - \int_a^b g(x, z)\tilde{f}'(x|z)dx
\]

where \( a \) and \( b \) denote the boundary of the support of \( X \). Assuming (A2), \( \tilde{f}(a|z) = \tilde{f}(b|z) = 0 \), then, \( \Psi(z) = E\{g(X, Z)|X|z\} = \{l(x|z)\text{ with } l(x|z) \text{ given by (13)} \} \). To motivate Theorem 1, note that inverting (13) gives

\[
\tilde{f}(x|z) = -\int_a^x l(x^*|z)f(x^*|z)dx^* = -E\{l(X|z)|X \leq x, Z = z\}F(x|z)
\]

Proof of Theorem

Theorem 1 essentially follows by the integration by parts argument above, provided we can show that the function \( \tilde{f}(x|z) \) in (15) is a density function that satisfies A2. Note A1 is satisfied since \( \tilde{f}'(x|z) = -l(x|z)f(x|z) \) by the fundamental theorem of calculus. To do so, let \( \Theta(u) \) denote a step function which is 1 for \( u \geq 0 \) and 0 for \( u < 0 \) and hence,

\[
\tilde{f}(x|z) = -\int_a^b \Theta(x-x^*)l(x^*|z)dP(x^*|z)
\]

integrating over \( x \),

\[
\int_a^b \tilde{f}(x|z)dx = \int_a^b \left[ \int_a^b -\Theta(x-x^*)dx \right] l(x^*|z)dP(x^*|z)
\]

where \( dP(x|z) \), is the probability measure of \( X \) given \( Z \). For the part in the square brackets,

\[
\int_a^b -\Theta(x-x^*)dx = \int_{x^*}^b -1dx = x^* - b
\]

Hence,

\[
\int_a^b \tilde{f}(x|z)dx = E\{l(X|Z)X|Z = z\} - bE\{l(X|Z)|Z = z\} = 1
\]

Since \( \tilde{f}(x|z) \) integrates to 1 and is non-negative by the inequality in (15), it is a density function. Next we show \( \tilde{f}(x|z) \) satisfies A2 when \( X \) is a continuous random variable. Since \( x^* \leq b \), then \( \Theta(b-x^*) = 1 \), hence

\[
\tilde{f}(b|z) = -\int_a^b l(x^*|z)dP(x^*|z) = -E\{l(X|Z)|Z = z\} = 0
\]

Similarly, since \( x^* \geq a \), then \( \Theta(a-x^*) = 1 \) only for \( x^* = a \),

\[
\tilde{f}(a|z) = -\int_a^a l(x^*|z)dP(x^*|z) = -l(a|z)P(X = a|Z = z)
\]

Since \( X \) is continuous, \( P(X = a|Z = z) = 0 \). This completes the proof.
Proof of Lemma 1.1

First we prove that Theorem 1 is satisfied when \( l(x|z) \) is monotonically increasing and (C1) \( E\{l(X|Z)|Z = z\} = 0 \) and (C2) \( E\{l(X|Z)X|Z = z\} = 1 \) for all \( z \). We split \( l(x|z) \) into a positive and negative part by defining two non-negative functions, \( l^+(x|z) = \max\{l(x|z),0\} \) and \( l^-(x|z) = \max\{-l(x|z),0\} \) such that, \( l(x|z) = l^+(x|z) - l^-(x|z) \). It follows from (C1) that,

\[
E\{l^+(X|Z)|Z = z\} = E\{l^-(X|Z)|Z = z\}
\]

This equality is satisfied by \( l^+(x|z) = l^-(x|z) = 0 \), however this solution violates (C2), hence the positive and negative parts are both non-zero. Since, \( l(x|z) \) is monotonically increasing there must be some value, \( c = c(z) \), on the support of \( X \), such that the positive part is zero for \( x < c \) and the negative part is zero for \( x \geq c \), i.e.

\[
l(x|z) = l^+(x|z)\Theta(x - c) - l^-(x|z)\{1 - \Theta(x - c)\}
\]

First consider the inequality in (15) when \( x < c \),

\[
\int_a^x l(x^*|z)dP(x^*|z) = -\int_a^x l^-(x^*|z)dP(x^*|z) \leq 0
\]

When \( x \geq c \),

\[
\int_a^x l(x^*|z)dP(x^*|z) = \int_c^x l^+(x^*|z)dP(x^*|z) - \int_a^c l^-(x^*|z)dP(x^*|z)
\]

The first part on the right hand side is \( \leq E\{l^+(X|Z)|Z = z\} \) and the second part is \( = E\{l^-(X|Z)|Z = z\} \) therefore, in both cases,

\[
\int_a^x l(x^*|z)dP(x^*|z) \leq 0
\]

Hence \( \hat{f}(x|z) \) \( \geq 0 \), so the inequality in (15) is satisfied. The proof is completed by verifying that the contrast function in (17) is monotonically increasing when \( v(x, z) \) is monotonically increasing or decreasing but not constant. This is fairly straight forward and we note that the decreasing case follows from the increasing case since (17) is invariant to replacing \( v(x, z) \) with \(-v(x, z)\).

Moment and Cumulant Functions of the ALSE intervention distribution

Consider a random variable, \( X \) with measure \( dP(x) \), mean \( \mu \), variance \( \sigma^2 \), and support \([a, b] \). The ALSE intervention density is,

\[
\hat{f}(x) = \int_a^b \Theta(x - x^*)\frac{\mu - x^*}{\sigma^2}dP(x^*)
\]

where \( \Theta(.) \) is the unit step function. The characteristic function of this density is

\[
\hat{\varphi}(t) = \int_a^b e^{itx} \hat{f}(x)dx
\]

\[
= \int_a^b \int_a^b e^{itx}\Theta(x - x^*)\frac{\mu - x^*}{\sigma^2}dP(x^*)dx
\]

\[
= \int_a^b \frac{\mu - x^*}{\sigma^2} \left[ \int_a^b e^{itx}\Theta(x - x^*)dx \right]dP(x^*).
\]
For the part inside the square brackets,
\[ \int_{a}^{b} e^{itx} \Theta(x - x^*) dx = \int_{x^*}^{b} e^{itx} dx = \frac{e^{itb} - e^{itx^*}}{it} \]

Hence,
\[ \tilde{\varphi}(t) = \int_{a}^{b} \frac{t - x^*}{it\sigma^2} \left\{ e^{itb} - e^{itx^*} \right\} dP(x^*) = \int_{a}^{b} \frac{x^* - \mu}{it\sigma^2} e^{itx^*} dP(x^*) \]
\[ = \frac{-1}{t\sigma^2} \left\{ \varphi'(t) - i\mu \varphi(t) \right\} \]

where \( \varphi(t) = E(e^{itX}) \) is the characteristic function of the density \( f \), with derivative \( \varphi'(t) = E(iXe^{itX}) \). Similarly, if the moment function \( M(t) = E(e^{tX}) \) exists, then the moment function of the ALSE intervention density is
\[ \tilde{M}(t) = \frac{1}{t\sigma^2} \left\{ M'(t) - \mu M(t) \right\} = \frac{M(t)}{t\sigma^2} \left\{ M'(t) - \mu \right\} \]
\[ = \exp \left\{ K(t) \right\} \left\{ \frac{1}{t\sigma^2} \left\{ K'(t) - \mu \right\} \right\} \]

where \( K(t) = \log \{ M(t) \} \). Hence, letting \( \tilde{K}(t) = \log \{\tilde{M}(t)\} \), the cumulant function of the ALSE intervention density is given by (24), where we note that the mean and variance are the first and second cumulants of \( K(t) \) respectively.

**Proof of Theorem 2**

To demonstrate symmetry of the ALSE transformation, we use the standard result that the characteristic function of a random variable is real if and only if the distribution of the corresponding random variable is symmetric about 0, see [Feller (1966), Chapter XV]. We let \( X \) be a symmetrically distributed random variable with finite mean, \( \mu \) and variance, \( \sigma^2 \) and write the transformed variable \( \tilde{X} \), which is distributed according to the ALSE intervention distribution associated with \( X \). It follows from (29) that,
\[ E_{\tilde{P}} \{ e^{it(X - \mu)} \} = \frac{-1}{t\sigma^2} \frac{d}{dt} E \{ e^{it(X - \mu)} \} \]

Here \( E \{ e^{it(X - \mu)} \} \) is the characteristic function of the random variable \( X - \mu \) which is symmetric about 0, and hence the RHS is real. The LHS is the characteristic function of the random variable \( \tilde{X} - \mu \) which must also be real, and hence symmetric about 0.

**ALSE intervention distribution for certain exposure distributions**

The Gamma distribution with shape parameter, \( \alpha \) and rate parameter, \( \beta \), and cumulants, \( \kappa_1 = \alpha / \beta \) and \( \kappa_2 = \kappa_1 / \beta \) and cumulant generating function,
\[ K(t; \alpha, \beta) = -\alpha \log \left( 1 - \frac{t}{\beta} \right) \]

Therefore, by (24),
\[ \tilde{K}(t; \alpha, \beta) = -(\alpha + 1) \log \left( 1 - \frac{t}{\beta} \right) \]
which happens to be $K(t; \alpha+1, \beta)$. Note the Chi-squared Distribution is a special case of the Gamma distribution with, $\alpha = k/2$ and $\beta = 1/2$.

The beta distribution, with shape parameters, $\alpha$, and $\beta$, has the density

$$f(x|\alpha, \beta) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha)\Gamma(\beta)} x^{\alpha-1}(1-x)^{\beta-1}$$

for $x \in [0,1]$ and 0 otherwise. The mean is $\mu = \alpha/(\alpha + \beta)$ and we note that $xf(x|\alpha, \beta) = \mu f(x|\alpha + 1, \beta)$, hence,

$$\tilde{f}(x|\alpha, \beta) = \int_0^x \frac{\mu - x^*}{\sigma^2} f(x^*|\alpha, \beta) dx^* = \frac{\mu}{\sigma^2} \{F(x|\alpha, \beta) - F(x|\alpha + 1, \beta)\}$$

The distribution function, $F(x|\alpha, \beta)$ has the property that

$$F(x|\alpha + 1, \beta) = F(x|\alpha, \beta) - \frac{\Gamma(\alpha + \beta)}{\alpha\Gamma(\alpha)\Gamma(\beta)} x^\alpha (1-x)^\beta$$

Therefore, using the fact that $\mu/\sigma^2 = (\alpha + \beta)(\alpha + \beta + 1)/\beta$, we recover the result, $\tilde{f}(x|\alpha, \beta) = f(x|\alpha + 1, \beta + 1)$.

The beta-prime distribution, with shape parameters, $\alpha$, and $\beta$, has the density

$$f(x|\alpha, \beta) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha)\Gamma(\beta)} x^{\alpha-1}(1+x)^{-\alpha-\beta}$$

for $x \geq 0$. Whilst the result for the beta-prime distribution can be derived in a similar way to the beta distribution, it is sufficient to verify that

$$\frac{d}{dx} f(x|\alpha + 1, \beta - 2) = \frac{\mu - x}{\sigma^2} f(x|\alpha, \beta)$$

The result follows since, by (13),

$$\frac{d}{dx} \tilde{f}(x|\alpha, \beta) = \frac{\mu - x}{\sigma^2} f(x|\alpha, \beta)$$

**Proof of Theorem 3**

For an efficient estimator of $\Psi$,

$$\hat{\Psi} = \Psi + n^{-1} \sum_{i=1}^n \phi(o_i) + o_p(n^{-1/2})$$

where $\phi(o_i)$ is the influence curve of $\Psi$ in [26]. Hence,

$$n^{1/2}(\hat{\Psi} - \Psi_S) = n^{-1/2} \sum_{i=1}^n w(z_i) l(x_i|z_i) \{y_i - m(x_i, z_i)\} + o_p(1)$$

Therefore the efficiency bound is

$$V = E \{w(Z)^2 l(X|Z)^2 \{Y - m(X, Z)\}^2 \}$$

$$= E \{w(Z)^2 l(X|Z)^2 E \{\{Y - m(X, Z)\}^2|X, Z\} \}$$

$$= E \{w(Z)^2 l(X|Z)^2 \sigma^2(X, Z) \}$$

$$= E \{w(Z)^2 E[l(X|Z)^2 \sigma^2(X, Z)|Z] \}$$
Minimizing $E\{l^2(X|Z)\sigma^2(X,Z)|Z = z\}$ subject to $E\{l(X|Z)|Z = z\} = 0$ and $E\{l(X, Z)|X|Z = z\} = 1$. Using Lagrange multipliers, $\lambda_1$, $\lambda_2$, which are both constant given $Z = z$,

$$\int l^2(x|z)\sigma^2(x, z) - 2\lambda_1 l(x|z) - 2\lambda_2 \{l(x|z)x - 1\}dP(x|z)$$

Differentiating the Lagrangian with respect to $l(x|z)$ and setting equal to zero gives.

$$l(x|z) = \frac{\lambda_1 + \lambda_2 x}{\sigma^2(x, z)}$$

Applying the two constraints fixes $\lambda_1$ and $\lambda_2$, giving the contrast function stated in the main theorem. Next we consider optimizing for $w(z)$ under the constraint $E\{w(Z)\} = 1$. Again, the use of Lagrange multipliers gives

$$\int w(z)^2 E\{l^2(X|Z)\sigma^2(X, Z)|z\} - 2\lambda_3 \{w(z) - 1\}dP(z)$$

and differentiating the Lagrangian with respect to $w(z)$ and setting equal to zero gives

$$w(z) = \lambda_3 \frac{1}{E\{l^2(X|Z)\sigma^2(X, Z)|Z = z\}}$$

The constant, $\lambda_3$ is fixed by the constraint, completing the proof.