Assessing the Causal Effect of Policies: An Example Using Stochastic Interventions

Abstract: Assessing the causal effect of an exposure often involves the definition of counterfactual outcomes in a hypothetical world in which the stochastic nature of the exposure is modified. Although stochastic interventions are a powerful tool to measure the causal effect of a realistic intervention that intends to alter the population distribution of an exposure, their importance to answer questions about plausible policy interventions has been obscured by the generalized use of deterministic interventions. In this article, we follow the approach described in Díaz and van der Laan (2012) to define and estimate the effect of an intervention that is expected to cause a truncation in the population distribution of the exposure. The observed data parameter that identifies the causal parameter of interest is established, as well as its efficient influence function under the non-parametric model. Inverse probability of treatment weighted (IPTW), augmented IPTW and targeted minimum loss-based estimators (TMLE) are proposed, their consistency and efficiency properties are determined. An extension to longitudinal data structures is presented and its use is demonstrated with a real data example.

Keywords: causal inference, stochastic interventions, TMLE

1 Introduction

Current approaches to causal inference [1–4] define causal parameters in terms of the distribution of variables generated by a system in which the stochastic nature of a set of variables is intervened on. Such interventions may be defined in various ways: static, dynamic, or stochastic. A static intervention is one in which the treatment is set to a given fixed value deterministically, while a dynamic intervention allows such value to depend on variables that precede it causally. Static interventions have also been called deterministic [5] or atomic [1].

In spite of their widespread use, deterministic interventions (whether static or dynamic) do not provide an appropriate framework to answer causal questions about phenomena that are not subject to direct intervention. Feasible interventions often interact with other factors (e.g., a medication has impact in several organs), fail to put the exposure of interest into a deterministic state (e.g., it is unrealistic to set an individuals’ exercise regime according to a deterministic function), or are the result of implementing policies that target stochastic changes in the behavior of a population (e.g., the use of mass media messages advertising condom use as a means of prevention of HIV infection is a deterministic treatment at the community level that renders a stochastic one at the individual level, because each individual will react stochastically to the intervention depending upon exogenous observed or non-observed factors, see McAlister [6]).

In general [5], an intervention can be simply defined as an external manipulation of a causal system, whether that manipulation is deterministic or stochastic. A static intervention corresponds to an alteration
of the causal system in which the density of the exposure is changed to a degenerate one. One can also intervene in the exposure by changing its density in any arbitrary way, which leads to a natural generalization of the counterfactual framework of Rubin [3]. This general approach is perhaps of more interest from a policy-making standpoint: if the counterfactual distribution of the exposure reflects the expected changes induced by a hypothetical intervention policy, the intervened model contains all the information about the causal effect of the intervention in the distribution of the outcome.

Stochastic interventions also provide a new, natural way of defining causal parameters for any type of exposure (e.g., continuous ones), regardless of its support and dominating measure. Thus far this was only possible through the use of misspecified parametric models or the use of marginal structural models [7]. Some advantages of stochastic interventions with respect to marginal structural models include weakening the positivity assumption and robustness with respect to misspecification of the model for the treatment mechanism.

Because stochastic interventions generalize static and dynamic interventions, and since several intervention policies are not representable in terms of either static or dynamic interventions, the development of methods for identification and estimation of parameters defined in terms of stochastic interventions is of great importance to the causal inference research community.

Among the few works dealing with the mathematical formalization of stochastic interventions figure Didelez et al. [8] and Dawid and Didelez [9], who provide a systematic and comprehensive discussion of identification of parameters of stochastic, dynamic, and static interventions, studying them from a decision-theoretic viewpoint, exploiting representations of causal systems in terms of regime indicators and influence diagrams, and presenting a parallel between their theory and existing theory for dynamic, non-stochastic regimes. Tian [10] shows that the identification of sequential intervention, whether stochastic or not, can be reduced to identification of a specific set of sequential static interventions, for which there are complete identifications algorithms available in the literature. It is therefore no surprise that identification of our parameter in Section 2.2 requires no further assumptions than those required for identification of a static intervention.

Stochastic interventions arise in applications either inspired by a deterministic intervention or because they are of interest in themselves. The most popular example of the former situation is given by the definition of natural direct effects, in which the effect of intervention in the dichotomous version of the treatment variable. This dichotomization represents current common practice: in Section 3 we will discuss the differences between this approach and the method presented in this article. Cain et al. [18] briefly discuss a stochastic intervention in the context of comparing dynamic treatment regimes for HIV-infected patients. The regimes they discuss are of the type “initiate treatment within $m$ months after the recorded CD4 cell count first falls below $x$. They are interested in an atomic intervention in the CD4 cell count $X$, and a discrete uniform $\{0, m\}$ post-intervention distribution for the number of months before treatment $M$. Such intervention is discussed in more detail by Young et al. [19].

Among the applications in which stochastic interventions arise as an interest in themselves, Díaz and van der Laan [20] considered the effect of an intervention in a population of people over 55 years of age that aimed to change the distribution of the amount of energy spent in leisure time physical activity.
on all cause mortality. In this article, we will analyze the effect of an intervention that intends to reduce air pollution levels below a certain threshold, but allows a stochastic distribution of air pollutants below such threshold. The claims about identifiability and properties of the estimators presented in this article are valid only for this stochastic intervention, although they can be generalized to a broader class of interventions.

Consistent and efficient estimation of statistical parameters in semiparametric models has been studied by Bickel et al. [21], van der Laan and Robins [22], Rose and van der Laan [23], and Tsiatis [24], among others. In particular, Rose and van der Laan [23] provide a very valuable link between efficient estimation theory in semiparametric models and causal inference, empowering researchers with tools to define a causal parameter of interest, propose a model for the distribution of the data, and compute an efficient, targeted estimate of the parameter of interest under that model. Proposal of a model for the distribution of the data starts with a completely nonparametric model that can only be reduced in size if real knowledge about the functional form of the distribution of the data is obtained. Parametric assumptions often made for the sake of computational convenience are not allowed: they do not represent knowledge about the phenomena under study and therefore may result in biased estimates.

In this article, we will demonstrate the use of stochastic interventions to assess the effect of a (hypothetical) law that enforces pollution levels below a certain cutoff point. For estimation of causal effects, we use efficiency theory in semiparametric models, and in particular the targeted minimum loss based estimation road map as described by Rose and van der Laan [23].

The article is organized as follows. In Section 2, we define the observed and counterfactual data, as well as the causal and statistical parameter and its efficient influence function. In Section 3, we discuss how this problem would be tackled with existing methods and argue that the conclusions of such methods are misleading. In Section 4, we present three estimators of the statistical parameter of interest: an inverse probability of treatment weighted estimator (IPTW), an augmented IPTW that solves the efficient influence curve equation, and a targeted minimum loss based estimator (TMLE). Section 5 provides an extension to longitudinal data settings and illustrates its use to measure the effect of NO2 concentrations in the air on asthma symptoms in children between 6 and 11 years of age. Finally, Section 6 provides some concluding remarks and directions of future research.

2 Observed data, counterfactuals and parameter of interest

2.1 Causal and statistical models

Consider an experiment in which an exposure variable $A$, a continuous or binary outcome $Y$, and a set of covariates $W$ are measured for $n$ randomly sampled subjects, and the outcome is measured subject to an indicator of missingness denoted by $C$. Let $O = (W, A, C, Y)$ represent a random variable with distribution $P_0$, and $O_1, \ldots, O_n$ represent $n$ i.i.d. observations of $O$. Assume that the following nonparametric structural equation model (NPSEM, Pearl [1]) holds:

$$W = f_W(U_W); \quad A = f_A(W, U_A); \quad C = f_C(A, W, U_C); \quad CY = f_Y(A, W, U_Y),$$

(1)

where $U_W$, $U_A$, $U_C$ and $U_Y$ are exogenous random variables assumed to satisfy the randomization assumption $(U_C, U_A) \perp\!\!\!\perp U_Y|W$. The true distribution of $O$ can be factorized as

$$P_0(O) = P_0(W)P_0(A|W)P_0(C|A, W)\{P_0(Y|A, W, C)\}^C \{I(CY = 0)\}^{1-C},$$

(2)

and we denote $g_0(A|W) = P_0(A|W)$, $\phi_0(A, W) = P_0(C = 1|A, W)$, and $\bar{Q}_0(A, W, C) = E_0(Y|A, W, C)$.

In the next sections, we will use this data structure to define a causal and statistical parameter of interest, find its efficient influence curve, Bickel et al. [21], van der Laan and Robins [22], and establish the asymptotic properties of estimators that solve the efficient curve equation.
2.2 Causal and statistical parameters

Assume that the researcher is interested in estimating the effect of a policy that will cause a truncation of the exposure, relocating the probability mass originally located above certain threshold $\delta_1$ in an interval $(\delta_1, \delta_2)$, where $\delta_1 = \delta_2 - \varepsilon$ for some small $\varepsilon$. Formally put within the causal framework of Pearl [1], such policy can be described by considering the modified system

$$W = f_W(U_W); \quad A_{P_1} = T_{g_1}(f_\delta(W, U_\lambda), W); \quad C_{P_1} = 1; \quad Y_{P_{1,1}} = f_Y(A_{P_1}, W, U_Y),$$

where $g_1$ denotes a user-given (but possibly unknown, e.g., one could set $g_1 = g_{0_1}$) conditional distribution of $A$ given $W$,

$$T_{g_1}(A, W) = \begin{cases} G_1^{-1}(G_1(A)) & \text{if } A < \delta_1 \\ G_1^{-1}\left( G_1(A) - G_1(\delta_1 | W) + G_1(\delta_1 | W) W \right) & \text{if } A \geq \delta_1, \end{cases}$$

and $G_1$ denotes the distribution function corresponding to $g_1$. The distribution of $A_{P_1}$ is given by

$$P_\delta(g_1)(A_{P_1} = a | W) = \begin{cases} g_1(a | W) & \text{if } a < \delta_1 \\ g_1(a | W) K(g_1)(W) & \text{if } \delta_1 \leq a \leq \delta_2 \\ 0 & \text{otherwise}, \end{cases}$$

where

$$K(g)(W) = \frac{1 - G(g_1 | W)}{G(\delta_1, \delta_2 | W)}$$

and in an abuse of notation $G(\delta_1, \delta_2 | W) = \int_{\delta_1 \leq a \leq \delta_2} g(a | W) d\mu(a)$. This intervention has two consequences on the distribution of the exposure: (i) it changes the distribution of values of $A$ below $\delta_1$ from $g_0$ to $g_1$ and (ii) it relocates the values of $A$ above $\delta_1$ between $\delta_1$ and $\delta_2$ according to distribution (5). As special case, we will consider the case $g_1 = g_0$, which is of particular interest when we want to assess the effect of policies that enforce the value of certain exposure below a pre-specified level. In such cases, the distribution of the set of individuals that already comply with the enforced cutoff is expected to remain unchanged, making consequence (1) void.

Under the randomization assumption, the expectation of the outcome $Y_{P_{1,1}}$ is identified as a function of the observed data generating mechanism $P_0$ as

$$\Psi(P_0) = E(Y_{P_{1,1}}) = E_{g_0}(Q_0(A, W, 1) \times M(g_1)(A, W)), \quad (6)$$

where $M(g)(A, W) = I_{\delta_0}(A) + I_{\delta_0, \delta_1}(A) \times K(g)(W)$, $I_{\delta_0}(A) = I(A < \delta_1)$ and $I_{\delta_0, \delta_1}(A) = I(\delta_1 \leq A \leq \delta_2)$. The true value of this parameter will be denoted $\psi_0 = \Psi(P_0)$. This identification result follows from the following argument. The usual consistency assumption $(A = a, C = 1) \Rightarrow Y_{a,1} = Y$ implies $(A_{P_1} = a, C = 1) \Rightarrow Y_{P_{1,1}} = Y_{a,1}$, therefore $P(Y_{P_{1,1}} = y | A_{P_1} = a, C = 1, W = w) = P(Y_{a,1} = y | A_{P_1} = a, C = 1, W = w)$. It is easy to verify that $(U_\lambda, U_\varepsilon) \perp \perp U_Y | W$ implies $(A_{P_1}, C) \perp \perp Y_{a,c} | W$ for all $a, c$. Thus $P(Y_{a,1} = y | A_{P_1} = a, C = 1, W = w) = P(Y_a = y | W = w)$, which from standard arguments for identification of static interventions (see for example Pearl [1]) can be shown to be identified by $P(Y = y | A = a, C = 1, W = w)$. This result can also be derived using the “G-recursion” formula, presented by Dawid and Didelez [9], which generalizes the G-computation formula for identifying the effect of dynamic regimes [25]. It can also be shown that the assumptions stated here are equivalent to the assumption of “simple stability” as defined by Dawid and Didelez [9], which generalizes the (sequential) randomization assumption to the case of stochastic interventions.

Parameter $\psi_0$ is a weighted mean of $Q_0(A, W, 1)$ (with respect to the joint distribution of $A$ and $W$), in which values of $Q_0(A, W, 1)$ for which $A < \delta_1$ receive weight one, values for which $\delta_1 \leq A \leq \delta_2$ receive weight $K(g_1)(W)$, and values for which $A > \delta_2$ receive weight 0. This makes intuitive sense; if the portion of the population whose exposure is originally above $\delta_2$ is relocated in exposure levels in $[\delta_1, \delta_2]$, the expected
outcome of individuals in $[\delta_1, \delta_2]$ should be reweighed by $K(g_t)(W)$, and the portion above $\delta_2$ should be reweighed by zero, given that no portion of the population will fall in that region after the intervention.

As a consequence of the formal equivalence between the counterfactual and the nonparametric structural equation model frameworks ([1], section 7.4.4.), all the results presented in this article can be derived under either paradigm. Furthermore, parameter (6) is a purely statistical parameter defined as the expectation of the outcome under a different distribution of $A$ given $W$ and can therefore be of interest in itself, without any underlying causal assumption or interpretation. In the following sections, we deal with estimation of (6) under a nonparametric model.

### 2.3 Efficient influence curve

The efficient influence curve is a key element in semiparametric efficient estimation, since it defines the linear approximation of any efficient and regular asymptotically linear estimator and therefore provides an asymptotic bound for the variance of all regular asymptotically linear estimators Bickel et al. [21]. We limit the discussion to efficient estimation of parameter (6) when $g_t = g_0$; the case of a user given function $g_t$ is easier and can be studied using similar arguments.

**Lemma 1.** The efficient influence curve of parameter (6) when $g_t = g_0$ is given by

$$D(P_0)(O) = \frac{C}{\phi_0(A, W)} M(g_0)(A, W)(Y - Q_0(A, W, 1))$$

$$+ 0$$

$$+ M(g_0)(A, W) \left\{ Q_0(A, W, 1) - \frac{E_{P_0}\{Q_0(A, W, 1)I_{\delta_1, \delta_2}(A)|W\}}{G_0\{\delta_1, \delta_2|W\}} \right\}$$

$$+ E_{P_0}\{Q_0(A, W, 1)I_{\delta_1, \delta_2}(A)|W\} - E_{P_0}\{Q_0(A, W, 1)M(g_0)(A, W)|W\}$$

$$+ E_{P_0}\{Q_0(A, W, 1)M(g_0)(A, W)|W\} - \Psi(P_0).$$

Where the terms (7)–(10) are denoted by $D_1(P_0)$, $D_2(P_0)$, $D_3(P_0)$, and $D_4(P_0)$; respectively, and correspond to the orthogonal decomposition of the efficient influence curve implied by the factorization of the likelihood in eq. (2).

This decomposition of the score is going to be useful later on during the construction of a targeted maximum likelihood estimator of $\psi_0$, to define the correct parametric fluctuations. The following lemma provides the conditions under which an estimator that solves the efficient influence curve equation is consistent.

**Lemma 2.** Let $D(O\{Q, g, \phi, \psi_0\}$ be the estimating equation implied by the efficient influence function of Lemma 1:

$$D(O\{Q, g, \phi, \psi_0\} = \frac{C}{\phi(A, W)} M(g)(A, W)(Y - Q(A, W, 1)) + M(g)(A, W)$$

$$\times \left\{ Q(A, W, 1) - \frac{E_P\{Q(A, W, 1)I_{\delta_1, \delta_2}(A)|W\}}{G\{\delta_1, \delta_2|W\}} \right\} + \frac{E_P\{Q(A, W, 1)I_{\delta_1, \delta_2}(A)|W\}}{G\{\delta_1, \delta_2|W\}} - \psi_0. $$

We have that $E_{P_0}D(O\{Q, g, \phi, \psi_0\} = 0$ if and only if $K(g) = K(g_0)$ and either $Q = Q_0$ or $\phi = \phi_0$.

As a consequence of Lemma 2, a substitution estimator of $\Psi(P_0)$ that solves the efficient influence curve equation will be consistent if and only if $K(g)$ and $Q_0$ or $\phi_0$ are estimated consistently, and it will be efficient if and only if all of the estimators for $K(g_0)$, $Q_0$, and $\phi_0$ are consistent. The robustness of this estimating equation is then tied to robustness of the estimator for $K(g_0)$. This consistency condition on
initial estimator \(g_n\) is weaker than the conditions needed for other methods for continuous exposures \(\text{e.g.},\) marginal structural models Neugebauer and van der Laan \([7]\); we only need an estimator \(g_n\) that is consistent in the sense that \(K(g_n) \rightarrow K(g_0)\), which is much weaker than the condition of \(g_n \rightarrow g_0\) required for marginal structural models. This is because \(K(g_0)\) only depends on the conditional probabilities \(G_1(\delta_1|W)\) and \(G(\delta_1, \delta_2|W)\), which can be consistently estimated by a misspecified estimator of the density.

An additional advantage over marginal structural modeling and other methods for continuous variables \([26]\) is given by the positivity assumption needed to identify and estimate the parameter of interest. The positivity assumption required to estimate marginal structural models is

\[
\sup_{a \in A} \frac{h(a)}{g_0(a|W)} < \infty, P_0 - a.e.,
\]

for a user-specified weight function \(h\). The function \(h(a) = 1\) is commonly used, since it implies giving equal weights to all the possible treatment values. The positivity assumption needed to identify and estimate our parameter of interest is given by

\[
G_0(\delta_1, \delta_2|W) > 0, P_0 - a.e.,
\]

which is a condition that depends on the choice of the interval \((\delta_1, \delta_2)\) and its probability under \(G_0\) and is thus more likely to be true than positivity of the density \(g_0\) for all the values \(a \in \mathcal{A}\).

### 3 Comparison with the standard approach

An alternative formulation of the causal problem of assessing the effect of a truncation in the exposure, which is the current standard in applications of causal inference methods \([27-30]\), is given by the use of a dichotomous version \(A^* = I(A < \delta_2)\) of the continuous treatment variable. The effect of a truncation of \(A\) is evaluated in terms of the static intervention \(A^* = 1\), and the parameter is defined as \(E[E(Y|A^* = 1, W)]\), which corresponds (as proven by Stitelman et al. \([17]\)) with a stochastic intervention on \(A\) in which \(g_0\) is changed to

\[
P_\delta(g_0)(A_p = a|W) = \left\{ \begin{array}{ll} g_0(a|W)/G(\delta_2|W) & \text{if } a < \delta_2 \\ 0 & \text{otherwise} \end{array} \right. \quad \text{(12)}
\]

which is equal to eq. (5) only if \(G(\delta_1|W) = 0\). This means that \(E[E(Y|A^* = 1, W)]\) measures the effect of a policy that will cause a truncation in the exposure, but will relocate the mass of the non-compliers \(\text{i.e., } G(\delta_2|W)\) across all the values below \(\delta_2\). As a consequence, the two parameters assess policies with different hypothetical effects on the density of the exposure; it is the researcher’s responsibility to judge which option is a more likely post-intervention distribution for the policy that is being evaluated.

For instance, in Section 5.2 we estimate the effect of a policy that enforces pollutant levels below a predefined threshold. Under such a policy, individuals polluting above the threshold will only have an incentive to reduce their pollution levels to a value that is in accordance with the policy, having no further incentive to go below the enforced cutoff point once they have reached it. Therefore, the most likely post-intervention distribution for this policy is one that locates the probability mass associated to the non-compliers around the cutoff point, i.e., intervention (5). The use of intervention (12) in this example could lead to misleading conclusions. As an example, consider the following data generating mechanism

\[
\begin{align*}
W_1 &\sim U(0, 1); & W_2 &\sim \text{Ber}(0.7); & W_3 &\sim N(W_1, 0.25 \exp(2W_1)) \\
W_1 &\sim U(0, 1); & W_2 &\sim \text{Ber}(0.7); & W_3 &\sim N(W_1, 0.25 \exp(2W_1)) \\
A &\sim \beta(S_1(W), S_2(W))
\end{align*}
\]

\[
Q(A, W) = \expit\{1 + W_1 + 1.5A + 2AW_1 + 0.5AW_2 - 2W_1W_2 + 0.2W_1W_3\}.
\]
where we consider four different values for $S_1$ and $S_2$: (1) $S_1(W) = S_2(W) = S(W)$, (2) $S_1(W) = S(W)$ and $S_2(W) = \expit(S(W))$, (3) $S_1(W) = \expit(S(W))$ and $S_2(W) = S(W)$; and (4) $S_1(W) = \expit(S(W))$ and $S_2(W) = \expit(S(W))$. For $S(W) = 2.5 + 0.6W_1 + 0.3W_2W_3 - 0.2W_1W_3 - 0.1(1 - W_2)W_1$. This four scenarios provide four different shapes of the beta distribution: (1) symmetric bell-shaped, (2) skewed to the left, (3) skewed to the right, and (4) symmetric U-shaped. Table 1 shows the parameter $E(Y_{PS} - Y)$ under interventions (5) and (12) for $(\delta_1, \delta_2) = (0.8, 0.9)$ and the four data generating mechanisms, providing a situation in which the conclusions obtained from the two analyses are very different. In this example, the two effects are fairly similar when the exposure would lead to misleading results, particularly for models (3) and (4). This numerical example provides a situation in which it is crucial to be clear about the hypothesized shape of the post-intervention distribution. The intervention implied by a dichotomization, usually used in practice, would lead to erroneous conclusion if the true post-intervention distribution is that of a truncation.

### Table 1 Results of a numerical example

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Data generating mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>(5)</td>
<td>-0.0001</td>
</tr>
<tr>
<td>(12)</td>
<td>-0.0009</td>
</tr>
</tbody>
</table>

## 4 Estimators

### 4.1 Initial estimators

In this section, we present three estimators for the parameter defined in eq. (6). The TMLE and the A-IPTW estimators solve the efficient influence curve equation and inherit the properties derived from Lemma 2. The IPTW is inefficient and will be consistent only if the estimator of $\phi_0$ is consistent. The TMLE is expected to perform better than the A-IPTW if the positivity assumption $\sup_{a \in \mathcal{A}} |\phi_0(a, W) > 0, - a.e.$ is violated. The finite sample properties of these estimators have been studied elsewhere [20, 23, 31].

The estimators presented in this section require initial estimates of $Q_0$, $g_0$ and $\phi_0$, which can be obtained through machine learning techniques, parametric or semiparametric models. The consistency of these initial estimators will determine the consistency and efficiency of the estimators of $\psi_0$, as discussed previously. Parametric models are commonly used because of their convenient analytical properties, but they encode assumptions on the distribution of the data that cannot be regarded as legitimate knowledge about the phenomenon under study and in general cause a large amount of bias in the estimated parameter. Simulations investigating the magnitude of the bias in causal parameter estimates induced by misspecified parametric models can be found, for example, in Kang and Schafer [32], Rose and van der Laan [23], Díaz and van der Laan [20]. As an alternative, we recommend the use of machine learning techniques such as the super learner [33]. Super learner is a methodology that uses cross-validated risks to find an optimal estimator among a library defined by the convex hull of a user-supplied list of candidate estimators. One of its most important theoretical properties is that its solution converges to the oracle estimator (i.e., the candidate in the library that minimizes the loss function with respect to the true probability distribution). Proofs and simulations regarding these and other asymptotic properties of the super learner can be found in van der Laan et al. [34] and van der Laan and Dudoit [35]. We will assume that $g_0$ is estimated consistently in the sense that $K(g_n) \rightarrow K(g_0)$.

Influence curve-based variance estimators are provided for these three estimators. Consistency of the variance estimators also depends on the consistency of the initial estimators of $Q_0$, and $\phi_0$. These dependency can be avoided at the cost of computational time and effort by using bootstrapped estimates of the variance.
4.2 IPTW

Given an estimator \( g_0^0 \) of the exposure density \( g_0 \), and an estimator \( \phi_n^0 \) of the missingness mechanism, the IPTW estimator of \( \theta_0 \) is defined as

\[
\psi_{n,1} = \frac{1}{n} \sum_{i=1}^{n} \frac{C_i}{\phi_n^0(A_i, W_i)} M(g_0^0)(A_i, W_i) Y_i.
\]

The IPTW is an asymptotically linear estimator with influence curve

\[
D_{\text{IPTW}}(O|g_0, \phi_0, \psi_0) = \frac{C}{\phi_0(A, W)} M(g_0)(A, W) Y - \psi_0.
\]

therefore the variable \( \sqrt{n}(\psi_{n,1} - \psi_0) \) converges in distribution to \( N(0, P_0 D_{\text{IPTW}}^2(g_0)) \), whose variance can be estimated as the empirical variance of \( D_{\text{IPTW}}^2(O|g_n^0, \phi_n^0, \psi_{n,1}) \). This is asymptotically a conservative estimator of the variance of the IPTW, as proven in van der Laan and Robins [22].

4.3 Augmented IPTW

The augmented IPTW is the value \( \psi_{n,2} \) that solves the equation

\[
\sum_{i=1}^{n} D(O|\tilde{Q}_n^0, g_n^0, \phi_n^0, \psi_n) = 0,
\]

for initial estimates \( Q_n^0, g_n^0 \) and \( \phi_n^0 \) of \( g_0, g_0 \) and \( \phi_0 \).

\[
\psi_{n,2} = \frac{1}{n} \sum_{i=1}^{n} \frac{C_i}{\phi_n^0(A_i, W_i)} M(g_n^0)(A_i, W_i) \left\{ Y_i - \tilde{Q}_n^0(A_i, W_i, 1) \right\} + M(g_n^0)(A_i, W_i) \times \left\{ \tilde{Q}_n^0(A_i, W_i, 1) - \frac{E_{\hat{g}}[Q(A, W, 1)I_{\delta_1}\delta_2|A, W]}{G_n^0[\delta_1, \delta_2|W]} \right\} + \frac{E_{\hat{g}}[Q(A, W, 1)I_{\delta_1}\delta_2|A, W]}{G_n^0[\delta_1, \delta_2|W]}.
\]

Since the treatment mechanism is estimated with data adaptive techniques, expectations with respect to \( g_n^0 \) must be computed using numerical methods. If the initial estimators are consistent, the A-IPTW is an asymptotically linear estimator with influence curve \( D(O|Q_n^0, g_n^0, \phi_n^0, \psi_{n,2}) \). As in the case of the IPTW, the variable \( \sqrt{n}(\psi_{n,2} - \psi_0) \) converges in law to a random variable with distribution \( N\{0, P_0 D^2(O|Q_n^0, g_n^0, \phi_n^0, \psi_{n,2})\} \), whose variance can be estimated via the empirical variance of \( D^2(O|Q_n^0, g_n^0, \phi_n^0, \psi_{n,2}) \). Rose and van der Laan [23], Appendix 18, show that inference based on this variance estimator is valid only if \( \phi_n^0 \) is consistent, providing exact inference when \( Q_n^0 \) is consistent, and conservative inference when \( Q_n^0 \) is inconsistent.

4.4 Targeted minimum loss-based estimator

Targeted maximum likelihood estimation [36] is a loss-based semiparametric estimation method that yields a substitution estimator of a target parameter of the probability distribution of the data that solves the efficient influence curve estimating equation and thereby yields a double robust locally efficient estimator of the parameter of interest, under regularity conditions.

In order to define a targeted maximum likelihood estimator for \( \psi_0 \), we need first to define three elements: (i) A loss function \( L(Q) \) for the relevant part of the likelihood required to evaluate \( \Psi(P) \), which in this case is \( Q = (Q, g, Q_w) \). This function must satisfy \( Q_0 = \arg\min Q E_{P_0} L(Q)|O) \), where \( Q_0 \) denotes the true value of \( Q \); (ii) An initial estimator \( Q_n^0 \) of \( Q_0 \); (iii) A parametric fluctuation \( Q(\varepsilon) \) through \( Q_n^0 \) such that the linear span of \( \frac{d}{d\varepsilon} L(Q(\varepsilon)) \) contains the efficient influence curve \( D(P) \) defined in Lemma (1). These elements are defined below:

4.4.1 Loss function

As loss function for \( Q \), we will consider \( L(Q) = L_Y(Q) + L_g(g) + L_w(Q_w) \), where for continuous \( Y \) we set \( L_Y(Q) = \{Y - Q(A, W, C)\}^2 \), for binary \( Y \) we set \( L_Y(Q) = Y \log\{Q(A, W, C)\} + (1 - Y) \log\{1 - Q(A, W, C)\}, \)
\[ L_A(g) = -\log g(A|W), \text{ and } L_W(Q_W) = -\log Q_W(W). \] It can be easily verified that this function satisfies \( Q_0 = \arg\min_{Q} E_P L(Q)(O). \)

### 4.4.2 Parametric fluctuation

Given an initial estimator \( Q_n^k \) of \( Q_0 \), with components \((Q_n^k, g_n^k, Q_{W.n}^k)\), and an initial estimator \( \phi_0^0 \) of \( \phi_0 \), we define the \((k+1)\)th fluctuation of \( Q_n^k \) as follows:

- \( m(Q_n^{k+1}((\varepsilon_1), A, W)) = m(Q_n^k(A, W)) + \varepsilon_1 H_1^k(A, W) \)
- \( g_{k+1}((\varepsilon_1)|A|W) \propto \exp(\varepsilon_1 H_1^k(A, W))g_{n}^k(A|W) \)
- \( Q_{W.n}^{k+1}((\varepsilon_2)|W) \propto \exp(\varepsilon_2 H_2^k(W))Q_{W.n}^k(W), \)

where

\[ H_1^k(A, W) = \frac{C}{\phi_0^0(A, W)} M(g_{n}^k(A, W)), H_2^k(A, W) = D_3(P^k)(O), \text{ and } H_4(W) = D_4(P^k)(O), \]

with \( D_3 \) and \( D_4 \) defined as in Lemma 1, and \( m \) is the identity or logit function depending on whether the outcome is continuous or binary. Note that this fluctuation satisfies the condition \( D(P) \in \langle \frac{d}{dx}L(Q(x)) \mid x = 0 \rangle \), which is a key element of targeted minimum loss-based estimation.

### 4.4.3 Targeted maximum likelihood estimator

The TMLE is defined by the following iterative process:

1. Initialize \( k = 0 \).
2. Estimate \( \varepsilon \) as \( \varepsilon_{k}^0 = \arg\min_{\varepsilon} P_n L(Q_{n}^{k}((\varepsilon))). \)
3. Compute \( Q_{n}^{k+1} = Q_{n}^{k}((\varepsilon_{k}^0)). \)
4. Update \( k = k + 1 \) and iterate steps 2 through 4 until convergence (i.e., until \( \varepsilon_{k}^0 = 0 \))

First of all, note that the value of \( \varepsilon_2 \) that minimizes the part of the loss function corresponding to the marginal distribution of \( W \) in the first step (i.e., \( -P_n \log Q_{W.n}^k((\varepsilon_2)) \)) is \( \varepsilon_2^0 = 0 \). Therefore, the iterative estimation of \( \varepsilon \) only involves the estimation of \( \varepsilon_1 \). The \( k \)th step estimation of \( \varepsilon_1 \) is obtained by numerically minimizing \( P_n (L_1(Q_n^{k}((\varepsilon_1))) + L_A(g_{n}^{k}((\varepsilon_1)))). \)

The TMLE of \( \psi_0 \) is defined as \( \psi_{0,3} = \lim_{k \rightarrow \infty} \psi(P_n^k) \), assuming this limit exists. In practice, the iteration process is carried out until convergence in the values of \( \varepsilon_k \) is achieved, and an estimator \( Q_n^k \) is obtained. The variance of \( \psi_{0,3} \) can be estimated by the empirical variance of \( D^2(O(Q_n^k, g_n^k, \phi_0^0, \psi_{0,3})), \) which is a consistent estimator only if both \( \phi_0^0 \) and \( Q_n^k \) are consistent, is conservative if \( \phi_0^0 \) is consistent but \( Q_n^k \) is not, and is inconsistent in any other case.

### 5 Extension to longitudinal data and application

#### 5.1 Longitudinal interventions

Assume now that the observed data structure is as presented in Section 2, but now we have repeated measures in the sense that for each subject the observed variables were recorded at time points \( t = 1, \ldots, T \). That is, the observed data in this case can be described as a vector \( O = (W_t, A_t, C_t, C_t Y_t : t = 1, \ldots, T) = (O_t : t = 1, \ldots, T) \). We can now define a time-specific counterfactual outcome given by \( Y_{t,P,\delta} \), where the stochastic intervention of interest is performed by changing each time-specific exposure mechanism \( g_{t,0} \) to...
where we set \( m_\beta(t) = \beta \), and \( w(t) \) is a weight function initially set to \( 1/T \). For this case (usually called the intercept only model), our parameter of interest reduces to

\[
\beta_0 = \sum_{t=1}^{T} w(t) E_0(Y_{t,P_\beta}),
\]

which is the weighted average of the time-specific causal effects. This parameter provides a measure of the overall effect of a policy when applied repetitively at every time point. Parameters given by more complex marginal structural models motivated by different research questions can also be defined by an appropriate MSM, for example the expectation of the counterfactual outcome at the last time point in the study, which will provide a measure of the final effect of implementing a given policy during \( T \) units of time, or an MSM that takes measures the possible trend in the expectation of the counterfactual outcome.

The efficient influence curve of parameter (14) is given by the weighted average of the time point specific influence curves:

\[
D_\beta(O|\bar{Q}, g, \phi, \beta_0) = \sum_{t=1}^{T} w(t) D(O_t|\bar{Q}_t, g_t, \phi_t, \psi_{t,0}),
\]

where \( D \) is defined in eq. (11) and \( \bar{Q}_t, g_t, \phi_t \) and \( \psi_{t,0} \) denote the conditional expectation of the outcome, exposure mechanism, missingness mechanism, and expectation of the counterfactual outcome for each time-specific data structure. Estimators that solve the efficient influence curve equation

\[
\sum_{i=1}^{n} \sum_{t=1}^{T} w(t) D(O_t|\bar{Q}_t, g_t, \phi_t, \psi_{t,0}),
\]

inherit the consistency and efficiency properties of estimators mentioned in Lemma 2, where the consistency conditions are now replaced by consistency in the estimation of all the time-specific mechanisms \( \bar{Q}_{t,0}, g_{t,0} \) and \( \phi_{t,0} \). To estimate each of these initial parameters, we can choose to fit different estimators for each time point, or we can also choose to do smoothing over \( t \), by including it as a covariate in each of the conditional expectations and probabilities involved.

Estimation of the parameter in eq. (14) can now be performed by applying the estimators presented in Section 4 to a pooled data set in which time has been added as a covariate and each row corresponds to a specific subject time point combination. The IPTW estimator, for example, would now be given by

\[
\psi_{n,1} = \frac{1}{nT} \sum_{i=1}^{n} \sum_{t=1}^{T} \frac{C_t}{\phi^{0}_{n}(A_{it}, W_{it})} M(g_{n,t}^0(A_{it}, W_{it})) Y_{it},
\]

and the augmented IPTW by

\[
\psi_{n,2} = \frac{1}{nT} \sum_{i=1}^{n} \sum_{t=1}^{T} \left[ \frac{C_t}{\phi^{0}_{n}(A_{it}, W_{it})} M(g_{n,t}^0(A_{it}, W_{it})) Y_{it} - Q_{n,t}^0(A_{it}, W_{it}, 1) \right] + M(g_{n,t}^0(A_{it}, W_{it}))
\]

\[
\times \left\{ \frac{E_{g_{n,t}^0} (\bar{Q}_{n,t}(A, W, 1) I_{\delta_t, \delta_t}(A)|W_{it})}{G_{n,t}^0(I_{\delta_t, \delta_t}(A)|W_{it})} \right\} + \frac{E_{g_{n,t}^0} (\bar{Q}(A, W, 1) I_{\delta_t, \delta_t}(A)|W_{it})}{G_{n,t}^0(I_{\delta_t, \delta_t}(A)|W_{it})},
\]
which can be seen to solve eq. (16). The TML estimator is defined analogous to the definition given in
the previous section, with $\hat{Q}_k^n$, $H_{k1}$, $\phi_k^n$, $H_{k3}$, $Q_{kW}$, and $H_{k4}$ replaced by their $t$-specific counterparts. However, the same parameters $\varepsilon_1$ and $\varepsilon_2$ are used to fluctuate all these $t$-specific estimates. Estimation of $\varepsilon$ in step 2 of the iterative process that defines the TMLE is performed now with respect to the empirical distribution $P_{NT}$ given by the pooled dataset, and the estimating equation in Lemma (2) is replaced by its counterpart summing also over $t$ and with $t$-specific estimated values of $\hat{Q}_k^n$, $H_{k1}$, $\phi_k^n$, $H_{k3}$, $Q_{kW}$, and $H_{k4}$. The estimators of the variance of these estimators presented in the previous section can also be adapted to these longitudinal estimators. Remarks about consistency of the variance estimators of Section 4 carry on to these variance estimators.

5.2 Application

In this section, we present the results of applying the method for longitudinal data described in the previous section to assess the effect of a program that constrains air pollution levels on wheezing in children with asthma. These data were originally analyzed by Mann et al. [37] as part of the Fresno Asthmatic Childrens Environment Study (FACES). In the original paper, whose objective was to evaluate whether exposure to ambient pollution is associated with increased respiratory symptoms, wheeze was found to be associated with short-term exposures to NO$_2$ with an odds ratio of 1.10 (estimated through repeated measures logistic regression, C.I. (1.02, 1.20)) for a 8.7 parts per billion increase. This value, according to the authors, corresponds to the 90% percentile of the absolute value of daily differences in NO$_2$ across the study period. The data consisted of a sample of 315 children between 6 and 11 years of age who have active asthma. Reports of morning wheeze were collected for 14 days, up to three times a year, from December 2000 through March 2005, which lead to approximately 12 data panels for each child. For a comprehensive description of the study, the interested reader is referred to the original paper.

We are interested in investigating the effect of NO$_2$ concentrations measured 24 hours before each visit on the current presence of wheezing. The confounders we considered (i.e., $W$ variables) are gender, age, race, height, low birth weight, born prematurely, atopy, presence of eczema, rhinitis, mother smoked during pregnancy, whether child was ever breastfed, presence of asthma in father and mother, no smoking policy in the house, anyone smokes in the house, relative humidity, temperature, season of the year, whether the house is rented or owned and income.

We estimated the effect of a policy that enforces NO$_2$ levels below 28.15 ppb. We assume that such intervention will produce a change in the population distribution of the exposure corresponding to a relocation of the probability mass originally above 28.15 ppb between 26.05 and 28.15 ppb in the intervened population. The values 28.15 and 26.05 ppb correspond with the 85th and 80th percentile of the distribution of NO$_2$, respectively. The choice of these particular values corresponds to an intervention that may be achievable in practice.

If the objective is to perform a comparison of the prevalence of wheezing in the hypothetical intervened population with the prevalence in the current population, we can define a population intervention parameter $\psi^1_0$ as $\psi^1_0 = \nu_0 - \mu_0$, where $\mu_0 = E_{P_0}(Y)$. This parameter compares the expectation of the outcome under the policy of interest with its current expectation and therefore provides a measure of the gain obtained by implementing the policy.

Since we observed a coarsened version of $Y$, we cannot use the empirical mean as an estimator of $\mu_0$. Because estimation of this expectation is equivalent to estimation of the expectation of the outcome under the intervention $C = 1$, we suggest the use of the TMLE for static interventions as described in Rose and van der Laan [23, chapter 4]. Such estimator also utilizes initial estimators of $\phi_0(A, W)$ and $\hat{Q}_{0}(A, W, C)$ and is double robust under misspecification of either model. For further details about the properties and implementation the TMLE for $\mu_0$, the reader is referred to the original sources.
For a given estimator \( \psi_n \) of \( \psi_0 \), and an asymptotically linear estimator \( \mu_n \) of \( \mathbb{E}_{\psi_0}(Y) \) with influence curve \( D_{\psi_0}(P) \), an asymptotically linear estimator of \( \psi_0 \) is given by \( \psi_n^1 = \psi_n - \mu_n \). Its influence curve can be computed as \( D_{\psi_0}(P)(O) = D_{\psi}(P)(O) - D_{\mu}(P)(O) \), and its variance can be estimated through the sample variance of \( D_{\psi_0}(P)(O) \). Here \( D_{\mu}(P)(O) \) represents the influence curve of each of the estimators defined in Section 4. The estimates of \( \psi_0^1 \) and their standard errors are presented in Table 2. Confidence intervals and p-values for hypothesis testing can be computed based on the normal approximations for asymptotically linear estimators described in Section 4. In light of the theoretical properties of these estimators, we rely on the TMLE and A-IPTW to measure the effect of the intervention of interest. The estimated value of \( \psi_0^1 \) means that under a policy that enforces places with NO\(_2\) levels above 28.15 to decrease their levels to some value in the interval (26.05, 28.15), the prevalence of wheezing in children with asthma between 6 and 11 years of age would be reduced by 0.50%. However, our estimated effect is not significant at a 95% confidence level. It is important to stress that lack of significance does not imply inexistence or epidemiological irrelevance of the effect, it only implies that there is not enough evidence in this particular data set to conclude that the effect is different from zero.

<table>
<thead>
<tr>
<th></th>
<th>TMLE</th>
<th>A-IPTW</th>
<th>IPTW</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \psi^1_0 )</td>
<td>0.50 (0.40)</td>
<td>0.15 (0.89)</td>
<td>0.99 (1.04)</td>
</tr>
<tr>
<td>( \psi_0 )</td>
<td>13.53 (0.56)</td>
<td>13.17 (0.99)</td>
<td>14.63 (1.14)</td>
</tr>
</tbody>
</table>

### 6 Conclusion

In this article, we propose a specific type of causal parameter defined by a stochastic intervention in terms of a truncation of the original distribution of the exposure. The approach presented in this article is suitable for assessing the effect of an intervention on a population before the intervention is put in place. We present an application example in which the effect of a potential policy enforcing pollution levels under certain threshold is measured. Our approach allows the estimation of the effect of potential policies that result in stochastic interventions (for example, because they fail to put every subject in a predefined exposure level).

We argue that our parameter makes more sense from a policy – and decision – making point of view as compared to current practice.

The stochastic interventions framework allowed us to naturally define an effect for a continuous exposure, which is a topic that has received little attention in the causal inference literature. Assumptions like the positivity assumption and the consistency of an initial estimator for the exposure mechanism are weakened as compared to those required for estimating other causal parameters for continuous or categorical exposures. Two consistent and efficient estimators for the parameter of interest were proposed, and their use was illustrated with an example.

The general stochastic intervention framework for defining causal effects allows the generalization of the policy assessment strategy to various problems, including longitudinal studies and time to event outcomes. Such generalizations would imply studying the influence function of the corresponding post-intervention outcome expectation, analogous to Section 2.3, and implementation of the targeted minimum loss-based estimator according to the general template as described, for example, by Rose and van der Laan [23].

An interesting direction of future research in this field is the development of methods to estimate the policy that must be put in place in order to obtain a pre-specified effect. For example, in the application of Section 5.2, it could be highly relevant for policy makers to estimate a threshold of NO\(_2\) that would reduce the prevalence of wheezing to an epidemiologically acceptable level. From a nonparametric point of view, this is a considerably harder estimation problem, since it entails inversion of the “dose-response” function of wheezing as a function of the law enforcement threshold.
References


