New bounds for the Probability of Causation in Mediation Analysis

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Abstract

An individual has been subjected to some exposure and has developed some outcome. Using data on similar individuals, we wish to evaluate, for this case, the probability that the outcome was in fact caused by the exposure. Even with the best possible experimental data on exposure and outcome, we typically can not identify this “probability of causation” exactly, but we can provide information in the form of bounds for it. Under appropriate assumptions, these bounds can be tightened if we can make other observations (e.g., on non-experimental cases), measure additional variables (e.g., covariates) or measure complete mediators. In this work we propose new bounds for the case that a third variable mediates partially the effect of the exposure on the outcome.

Keywords: Probability of Causation, Mediation, Causes of effects, Bounds

1 Introduction

Causality is a concept very common in real life situations. Is lung cancer caused by smoking? Was contaminated water causing cholera in London in 1854? Can the court infer sex discrimination in a hiring process? However, statisticians have been very cautious in formalizing this concept. One reason may be the complex definitions and methods implemented to study causality. Another explanation may be the difficulty of translating real life problems into mathematical notations and formulas. The first step should be to identify the causal question of interest. This can be assigned to one of two main classes: questions concerning the causes of observed effects, and questions concerning the effects of applied causes. This basic distinction, all too often neglected in the causal inference literature, is fundamental to identifying the correct definition of causation. To clarify this distinction, consider the following example. An individual, Ann, might be subjected to some exposure, X, and might develop some outcome, Y. For simplicity we take X to be a binary decision variable, denoting whether or not an individual is given the drug, and take the outcome variable Y also to be binary, coded 1 if the individual dies, and 0 if not. We denote by XA ∈ {0, 1} the value of Ann’s exposure, and by YA ∈ {0, 1} the value of Ann’s outcome. Questions about the effects of applied causes, “EoC”, are widely studied. For example, in medicine, randomized clinical trials are one of the most rigorous ways to assess the effect of a treatment in a population. In the EoC framework, at an individual level we would be interested in asking: “What would happen to Ann were she to be given the drug?” or “What would happen to Ann were she not to be given the drug?” . At the population level, a typical EoC query would be: “Is death caused by the drug?” In this framework, a straightforward way to assess the strength of causality is by comparing \( P_1 = P(Y = 1 \mid X ← 1) \) and \( P_0 = P(Y = 1 \mid X ← 0) \), the two outcome probabilities under the two different interventions [4]. This can be seen as a decision problem: we can compare

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these two different distributions for \( Y \), decide which one we prefer, and take the associated decision (give or withhold the drug). The difference \( P_1 - P_0 \) is known as the “Average Causal Effect”.

In contrast to EoC queries, that are mostly adopted to infer knowledge in the population, CoE questions invariably require an individual investigation. For example, suppose that Ann died after being given the drug. A typical CoE question might be phrased as: “Knowing that Ann did take the drug, and died, how likely is it that she would not have died if she had not had the drug?”. In this paper we will embed such causal queries in the counterfactual framework [7]. This is based on the idea that there exist potential variables. If \( X \) is the exposure and \( Y \) the outcome, the potential variable \( Y(x) \) is conceived as the value of \( Y \) that would arise if, actually or hypothetically, \( X \) were to be set to \( x \) \((X \leftarrow x)\). We denote the pair \((Y(0), Y(1))\) by \( Y(X) \). For an actual assignment \( X \leftarrow x \), we observe \( Y = Y(x) \). The potential variable \( Y(x') \), with \( x' \neq x \), is then not observable, but is supposed to describe what would have happened to the outcome \( Y \), if, counterfactually, we had assigned the different value \( x' \) to the exposure \( X \). Note particularly that it is never possible to observe fully the pair \( Y \).

The definition of a CoE causal effect is completely different from the EoC definition. It is typically framed in terms of the probability of causation (PC), also called probability of necessity [6]. Given that Ann took the drug and died, the probability of causation in Ann’s case is defined as:

\[
PC_A = P_A(Y_A(0) = 0 \mid X_A = 1, Y_A(1) = 1)
\]

where \( P_A \) denotes the probability distribution over attributes of Ann. For example, suppose that Ann’s children filed a criminal lawsuit against a pharmaceutical manufacturer claiming that their drug was the cause of her death. Using data on similar individuals, we would wish to evaluate, for this case, the probability that the outcome was in fact caused by the exposure.

In such a civil case, the required standard of proof is typically “preponderance of the evidence,” or “balance of probabilities,” meaning that the case would succeed if it can be shown that causation is “more probable than not,” i.e., \( PC_A > 50\% \). However, simplistic or ad hoc definitions and rules are widely and often wrongly applied in many courthouse. Given the possibly serious implications of the probability of causation, it is important to studying methods capable of producing accurate information.

From a statistical point of view, definition (1) involves the bivariate distribution of the two potential variables associated with the same subject. However, only one of these can ever be observed, the other then becoming counterfactual. For this reason, \( PC_A \) is generally not fully identifiable. We can however provide useful information as bounds between which \( PC_A \) must lie. Under appropriate assumptions, these bounds can be tightened if we can measure additional variables, e.g., covariates [1], or—in the case that unobserved variables confound the exposure-outcome relationship—gather data on other, nonexperimental, cases (Tian and Pearl [8].)

In this paper we propose a novel approach to bound the probability of causation in mediation analysis. Mediation aims to disentangle the extent to which the effect of \( X \) on \( Y \) is mediated through other pathways from the extent to which that effect is due to \( X \) acting directly on \( Y \). In §2 we revisit the basic framework where we have information only on exposure and outcome. In §3 we focus on two different mechanisms: complete and partial mediation. In the former, the exposure is supposed to act on the outcome only through the mediator, i.e., no direct effect is present. In the latter, both direct and indirect effects are considered. In §4 we compare the bounds obtained in §3 with those reviewed in §2, and in §5 we present our conclusions.

## 2 Starting Point: Simple Analysis

In this Section we discuss the simple situation in which we have information, as in Table 1, from a randomized experimental study that tested the same drug taken by Ann.

\[
P(Y = 1 \mid X \leftarrow 1) = 0.30
\]

\[
P(Y = 1 \mid X \leftarrow 0) = 0.12.
\]
|       | Die | Live | Total |
|-------|-----|------|-------|
| Exposed | 30  | 70   | 100   |
| Unexposed | 12  | 88   | 100   |

Table 1: Deaths in individuals exposed and unexposed to the same drug taken by Ann.

We see that, in the experimental population, individuals exposed to the drug ($X \leftarrow 1$) were more likely to die than those unexposed ($X \leftarrow 0$), by 18 percentage points. So can the court infer that it was Ann’s taking the drug that caused her death? More generally: Is it correct to use such experimental results, concerning a population, to say something about a single individual? This “Group-to-individual” (G2i) issue is discussed by Dawid [2]. The simple difference between (2) and (3) is not sufficient to infer causation for a single external individual.

To make progress we add a further assumption that the event of Ann’s exposure, $X_A$, is independent of her potential response pair $Y_A$:

$$X_A \perp \perp Y_A.$$  (4)

Property (4) parallels the “no-confounding” property $X_i \perp \perp Y_i$ that holds for individuals $i$ in the experimental study on account of randomization. We further suppose that Ann is exchangeable with the individuals in the experiment, i.e., she could be considered as a subject in the experimental population. On account of (4) and exchangeability, $PC_A$ in (1) reduces to $PC_A = P(Y(0) = 0 \mid Y(1) = 1)$—but we can not fully identify this from the data. In fact we can never observe the joint event ($Y(0) = 0; Y(1) = 1$), since at least one of $Y(0)$ and $Y(1)$ must be counterfactual. In particular, we can never learn anything about the dependence between $Y(0)$ and $Y(1)$. However, even without making any assumptions about this dependence, we can derive the following inequalities (Dawid et al. [4]):

$$\max \left\{ 0, 1 - \frac{1}{RR} \right\} \leq PC_A \leq \min \left\{ \frac{P(Y = 0 \mid X \leftarrow 0), P(Y = 1 \mid X \leftarrow 1)}{P(Y = 1 \mid X \leftarrow 1)}, \frac{P(Y = 1 \mid X \leftarrow 1)}{P(Y = 1 \mid X \leftarrow 0)} \right\},$$  (5)

where

$$RR = \frac{P(Y = 1 \mid X \leftarrow 1)}{P(Y = 1 \mid X \leftarrow 0)}$$  (6)

is the experimental risk ratio between exposed and unexposed. These bounds can be estimated from the experimental data using the population death rates in equations (2) and (3).

In many cases of interest (such as Table 1), we have

$$P(Y = 1 \mid X \leftarrow 0) < P(Y = 1 \mid X \leftarrow 1) < P(Y = 0 \mid X \leftarrow 0).$$

Then the lower bound in (5) will be non-trivial, while the upper bound will be 1, so vacuous. Since, in Table 1, the exposed are 2.5 times as likely to die as the unexposed ($RR = 30/12 = 2.5$), we have enough confidence to infer causality in Ann’s case, since $0.60 \leq PC_A \leq 1$.

### 3 Bounds in Mediation

In this Section we bound the probability of causation for a case where a third variable, $M$, is involved in the causal pathway between the exposure $X$ and the outcome $Y$. We first review the results of Dawid et al. [3] for the case of complete mediation, where no direct effect is present between exposure and outcome but all the effect is mediated by $M$. In addition we derive new bounds for $PC_A$ in mediation analysis when a partial mediation mechanism is in operation.
3.1 Complete mediation (Dawid et al. [3])

The case of no direct effect is intuitively described by Figure 1. Applications where this assumption might be plausible is in the treatment of ovarian cancer (Silber et al. [5]), where \( X \) represents management either by a medical oncologist or by a gynaecological oncologist, \( M \) is the intensity of chemotherapy prescribed, and \( Y \) is death within 5 years. We shall be interested in the case that \( M \) is observed in the experimental data but is not observed for Ann, and see how this additional experimental evidence can be used to refine the bounds on \( PC_A \).

\[
X \rightarrow M \rightarrow Y
\]

Figure 1: Graph representing a mediator \( M \), responding to exposure \( X \) and affecting response \( Y \). There is no direct effect, unmediated by \( M \), of \( X \) on \( Y \).

We now introduce \( M(x) \) to denote the potential value of \( M \) when \( X \leftarrow x \), and \( Y^*(m) \) to denote the potential value of \( Y \) when \( M \leftarrow m \). Then \( Y(x) := Y^*\{M(x)\} \). We define \( M := (M(0), M(1)) \) and \( Y^* := (Y^*(0), Y^*(1)) \).

We suppose that none of the causal mechanisms depicted in Figure 1 are confounded—expressed mathematically by assuming mutual independence between \( X, M \) and \( Y^* \) (both for experimental individuals, and for Ann). These assumptions imply no overall confounding (as in (4)), the Markov property \( Y \perp \perp X \mid M \), and the following bounds in this case of complete mediation:

\[
\max \left\{0, 1 - \frac{1}{RR} \right\} \leq PC_A \leq \frac{\mathrm{Num}}{P(Y = 1 \mid X \leftarrow 1)},
\]

where the numerator, \( \mathrm{Num} \), is given in Table 2. We see from (7) that knowing a mediator does not improve the lower bound. For the upper bound, one has to consider various scenarios according to different choices of the estimable marginal probabilities in Table 2.

| \( a \leq b \) | \( a > b \) |
|---|---|
| \( c \leq d \) | \( a \cdot c + (1 - d)(1 - b) \) | \( b \cdot c + (1 - d)(1 - a) \) |
| \( c > d \) | \( a \cdot d + (1 - c)(1 - b) \) | \( b \cdot d + (1 - a)(1 - c) \) |

Table 2: Numerator of upper bound for \( PC_A \) in complete mediation analysis. Here \( a = P(M(0) = 0) \), \( b = P(M(1) = 1) \), \( c = P(Y^*(0) = 0) \) and \( d = P(Y^*(1) = 1) \).

Note that, given the no-confounding assumptions, the entries in Table 2 are all estimable from the experimental data:

\[
\begin{align*}
a &= P(M = 0 \mid X \leftarrow 0) \\
b &= P(M = 1 \mid X \leftarrow 1) \\
c &= P(Y = 0 \mid M \leftarrow 0) \\
d &= P(Y = 1 \mid M \leftarrow 1).
\end{align*}
\]

3.2 Partial mediation

The situation described by Figure 1 is unlikely to hold in many real life situations. Situations such as that represented informally by Figure 2 that allow both direct and indirect effects, are more plausible. In this Section we derive new bounds for the probability of causation when a partial mediator is involved in the causal pathway. We now define \( Y^*(x, m) \) as the potential value of the outcome \( Y \) after setting both exposure, \( X \leftarrow x \), and mediator, \( M \leftarrow m \). Then \( Y(x) = Y^*(x, M(x)) \). We make the following assumptions, both for Ann and for the individuals in the experiment:
Figure 2: Graph illustrating a partial mediation mechanism between an exposure $X$, an outcome $Y$, and a mediator $M$

**A1:** $Y^*(x, m) \perp M \mid X$ (no $M-Y$ confounding)

**A2:** $Y^*(x, m) \perp X$ (no $X-Y$ confounding)

**A3:** $M(x) \perp X$ (no $X-M$ confounding).

Assumption A1 expresses independence, given $X$, between a potential value $Y^*(x, m)$, that would arise on setting exposure and mediator to particular values, and the pair of potential outcomes $(M(0), M(1))$. It can be seen as a strengthening of the univariate hypothesis $Y^*(x, m) \perp M(x) \mid X$.

Note that A1 and A2 are together equivalent to the single requirement:

**A12:** $Y^*(x, m) \perp (M, X)$.

Because we have supposed that Ann is exchangeable with the individuals in the experiment, we have

$$
PC_A = P(Y(0) = 0 \mid X \leftarrow 1, Y(1) = 1) = \frac{P(Y(0) = 0, Y(1) = 1 \mid X \leftarrow 1)}{P(Y(1) = 1 \mid X \leftarrow 1)}. \tag{8}
$$

Given the no-confounding assumptions, the denominator of (8) is $P(Y = 1 \mid X \leftarrow 1)$, which is estimable. However, the numerator of (8) involves the joint distribution of the pair $Y$ of potential outcomes, and this is not estimable from the data, in view of the fact that it is never possible to observe both $Y(0)$ and $Y(1)$ simultaneously. We can however bound this numerator in terms of estimable quantities, using the fact that, for any events $A$ and $B$, and any probability distribution $P$,

$$
\max \{P(A) + P(B) - 1, 0\} \leq P(A \cap B) \leq \min \{P(A), P(B)\}. \tag{9}
$$

Using (9), we can obtain an upper bound for the numerator as:

$$
P(Y(0) = 0, Y(1) = 1 \mid X \leftarrow 1) = P(Y^*(0, M(0)) = 0, Y^*(1, M(1)) = 1 \mid X \leftarrow 1)
= \sum_{m_0} \sum_{m_1} P(Y^*(0, m_0) = 0, Y^*(1, m_1) = 1 \mid M(0) = m_0, M(1) = m_1, X \leftarrow 1)
\times P(M(0) = m_0, M(1) = m_1 \mid X \leftarrow 1)
\leq \sum_{m_0} \sum_{m_1} \min \{P(Y^*(0, m_0) = 0 \mid M(0) = m_0, M(1) = m_1, X \leftarrow 1),
\quad P(Y^*(1, m_1) = 1 \mid M(0) = m_0, M(1) = m_1, X \leftarrow 1),
\quad P(M(0) = m_0 \mid X \leftarrow 1), P(M(1) = m_1 \mid X \leftarrow 1)\}
\times \min \{P(M(0) = m_0), P(M(1) = m_1)\}, \tag{10}
$$

on using assumptions A12 and A3. That is,

$$
P(Y(0) = 0, Y(1) = 1 \mid X \leftarrow 1) \leq
\min \{P(Y^*(0, 0) = 0), P(Y^*(1, 0) = 1)\} \times \min \{P(M(0) = 0), P(M(1) = 0)\} \tag{12}
+ \min \{P(Y^*(0, 0) = 0), P(Y^*(1, 1) = 1)\} \times \min \{P(M(0) = 0), P(M(1) = 1)\} \tag{13}
+ \min \{P(Y^*(0, 1) = 0), P(Y^*(1, 0) = 1)\} \times \min \{P(M(0) = 1), P(M(1) = 0)\} \tag{14}
+ \min \{P(Y^*(0, 1) = 0), P(Y^*(1, 1) = 1)\} \times \min \{P(M(0) = 1), P(M(1) = 1)\}. \tag{15}
$$
It can be shown that similarly applying the lower bound of (9) to (10) yields the same lower bound as obtained in §2 and §3.1 so that the lower bound is not improved by knowledge of a mediation mechanism.

Assumptions A12 and A3 allow us to estimate the terms (12)–(15) in the above upper bound from the data:

\[ P(\text{Y}^*(x, m) = y) = P(Y = y \mid X \leftarrow x, M \leftarrow m) \]

\[ P(M(x) = m) = P(M = m \mid X \leftarrow x). \]

4 Comparisons

In this Section we compare the bounds found in the simple analysis framework of §2 with those obtained by considering a complete mediation mechanism, as in §3.1, and those obtained by considering a partial mediation mechanism, as in §3. We focus on comparing these bounds to obtain the best information from the data.

The numerator of the upper bound for PC in (5), which ignores the mediator, may be written as

\[ \min\{\alpha + \beta, \gamma + \delta\} \]

where

\[ \alpha = P(Y^*(0, 0) = 0)P(M(0) = 0) \]

\[ \beta = P(Y^*(0, 1) = 0)P(M(0) = 1) \]

\[ \gamma = P(Y^*(1, 0) = 1)P(M(1) = 0) \]

\[ \delta = P(Y^*(1, 1) = 1)P(M(1) = 1). \]

We see that both (12) and (13) are smaller than or equal to \( \alpha \), while both (14) and (15) are smaller than or equal to \( \beta \). So the upper bound allowing for partial mediation, which is the sum of (12), (13), (14) and (15), cannot exceed \( 2(\alpha + \beta) = 2P(Y(0) = 0) = 2P(Y = 0 \mid X \leftarrow 0) \); and similarly cannot exceed \( 2P(Y = 1 \mid X \leftarrow 1) \). Thus, the upper bound for the numerator, when accounting for the mediator, can not exceed twice that obtained by ignoring it, as given by (5). However, as we will see in §4.1 it could be larger or smaller than that simpler bound. On the other hand, we do not obtain a different lower bound.

In the special case of complete mediation, \( Y^*(0, m) = Y^*(1, m), = Y^*(m) \), say. Thus the terms with \( m_0 \neq m_1 \) in (10) must be 0. This leads to the following upper bound:

\[ P(Y(0) = 0, Y(1) = 1 \mid X \leftarrow 1) \leq \]

\[ \min\{P(Y^*(0) = 0), P(Y^*(1) = 1)\} \times \min\{P(M(0) = 0), P(M(1) = 1)\} + \]

\[ + \min\{P(Y^*(1) = 0), P(Y^*(0) = 1)\} \times \min\{P(M(0) = 1), P(M(1) = 0)\}, \]

in agreement with Table 2. Since we have eliminated the terms (12) and (15) appearing in the general case, the upper bound obtained in this case of complete mediation is never bigger than that obtained from the general expression (12)+(13)+(14)+(15); nor, since (13) \( \leq \alpha \) while (14) \( \leq \beta \), can it be bigger than the bound (5) obtained on ignoring the knowledge of the complete mediation mechanism.

4.1 Examples

To show that, in the case of partial mediation, taking account of information about the mediator may, but need not, yield a tighter upper bound, we consider two cases with different experimental data as given respectively by Table 3 and Table 4.

Suppose now we can also observe a partial mediator \( M \). We might then observe the following probabilities, consistent with Table 3:

\[ P(Y^*(0, m) = y) = P(Y = y \mid X \leftarrow x, M \leftarrow m) \]

\[ P(M(x) = m) = P(M = m \mid X \leftarrow x). \]
### Table 3: Experimental data 1

|        | Die | Live | Total |
|--------|-----|------|-------|
| Exposed | 69  | 31   | 100   |
| Unexposed | 24  | 76   | 100   |

### Table 4: Experimental data 2

|        | Die | Live | Total |
|--------|-----|------|-------|
| Exposed | 78  | 22   | 100   |
| Unexposed | 32  | 68   | 100   |

\[
P(Y^*(0, 0) = 0) = 0.98 \quad \text{P}(Y^*(0, 1) = 0) = 0.165
\]
\[
P(Y^*(1, 0) = 0) = 0.315 \quad \text{P}(Y^*(1, 1) = 0) = 0.143
\]
\[
P(M(0) = 0) = 0.73 \quad \text{P}(M(1) = 0) = 0.981
\]

We then obtain: \(0.65 \leq PC_A \leq 0.81\) when accounting for the mediator, and \(0.65 \leq PC_A \leq 1\) when ignoring it. In this case, knowledge of the partial mediation mechanism is helpful in improving the upper bound.

On the other hand, suppose we observe the following probabilities, consistent with Table 4:

\[
P(Y^*(0, 0) = 0) = 0.98 \quad \text{P}(Y^*(0, 1) = 0) = 0.67
\]
\[
P(Y^*(1, 0) = 0) = 0.09 \quad \text{P}(Y^*(1, 1) = 0) = 0.27
\]
\[
P(M(0) = 0) = 0.04 \quad \text{P}(M(1) = 0) = 0.26
\]

We now obtain: \(0.59 \leq PC_A \leq 0.95\) when accounting for the mediator, but \(0.59 \leq PC_A \leq 0.88\) when ignoring it. So in this case knowledge of mediation has not been helpful.

## 5 Conclusions

Bounding the probability of causation in mediation analysis is an important problem for applications. By taking account of a complete mediation mechanism we can never do worse than by ignoring it. However, complete mediation is not always reasonable. In the case of partial mediation, the upper bound obtained by taking account of it may be greater or smaller than that obtained by ignoring it. We can thus compute both upper bounds and take the smaller.

This work has several possible extensions. It would be interesting to extend our theoretical formulas to cases combining information on both covariates and mediators. Another promising extension arises on making connections with copula theory, where PC can be obtained as a function of the estimable quantities \(P(Y(0) = 0)\) and \(P(Y(1) = 1)\) together with an appropriate copula.

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