The central role of the mediator process in mediation analysis

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Abstract

Causal mediation has traditionally been framed as the effect of an exposure on an outcome through some intermediate variable, where each variable is measured at three sequential time points. However, definitions of mediated effects and their corresponding identification assumptions generally ignore the fact that the mediator of interest is, in many if not most circumstances, a stochastic process indexed by time from baseline to follow-up. I demonstrate that the failure to account for the mediator process has profound implications for defining the relevant causal estimand of interest as well as its identification and estimation. Additionally, I introduce novel versions of direct and indirect effect definitions that account for the entire mediator process.

1 BACKGROUND

Time-varying variables play an important role in causal inference and must be accounted for appropriately. While early work in causal inference focused on the effect of an exposure defined at a fixed point in time, a vast body of work beginning with Robins [1986] has been developed to study the effects of time-varying exposures. The outcome is typically defined at some fixed time after baseline, and can be analyzed appropriately even if it comes from some underlying process. In many cases it can alternatively be handled as a longitudinal or time-to-event variable, thereby preserving more information. Confounders are typically considered as time-varying when the exposure is as well, and g-methods are necessary to correct for time-varying confounding.

By contrast, in mediation analysis, the mediator is traditionally considered at a fixed point in time between the exposure and outcome (though unfortunately in practice mediation analysis is often applied even when there is no such temporal ordering, which fails to yield any causal interpretation).

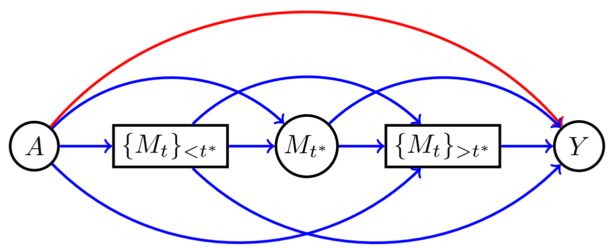
Generally, when the mediator is a time-varying process, even if only measured at a single time point, the typical identification assumptions for the natural direct/indirect effect (NDE/NIE) [Robins and Greenland, 1992, Pearl, 2001] will fail to hold. In particular, if the intermediate process does indeed mediate the effect of the exposure on the outcome, then instances of the mediator prior to its observation will typically be what are known as exposure-induced confounders. That is, earlier instances of the mediator will both be affected by the exposure, and be a common cause of the mediator at the time of its observation and the outcome. Furthermore, the traditional NIE definition does not capture the effect through the entire mediator process, but rather only at the time(s) at which it is observed. Here, I argue that the indirect effect defined with respect to the entire mediator process (regardless of whether it is actually observed) is the most relevant causal estimand, as the traditional NIE does not capture all effects through earlier and later instances of this process.

2 INNOVATION

Let A be the exposure defined at a fixed, common baseline, i.e., at time $t = 0$, Y be the outcome defined at a common follow-up time, say $t = 1$, without loss of generality, and M_{t^*} be an intermediate variable measured at some time $t^* \in (0, 1)$. In causal mediation analysis, the canonical indirect effect measure is the natural indirect effect (NIE): $NIE \equiv E[Y\{a, M_{t^*}(a)\}] - E[Y\{a, M_{t^*}(a^*)\}]$. This is the change in the mean outcome when exposure is set to level a, and the mediator at time t^* is changed from what it would have been under an intervention setting it to a to an intervention setting it to a^*. While other definitions of indirect effects have been proposed, these often lack a true interpretation as mediated effects [Miles, 2023].

These definitions of direct and indirect effects overlook the

Figure 1: A mediation DAG depicting the entire mediator process. The effect through the path in red is the NDE^F and the effect through the collection of paths in blue is the NIE^F.



possibility that the mediator observed at time t^* might be merely a snapshot in time of an underlying process occurring from baseline to follow-up. Suppose such a process exists, which I denote $\{M\}_{t\in(0,1)}$. Figure 1 displays a modified version of a directed acyclic graph (DAG) that accounts for the presence of such an underlying mediator process. The rectangular nodes indicate stochastic processes before and after time t^*, which are typically unobserved. Loosely speaking, when the arrows $A \to \{M_t\}_{<t^*}$, $\{M_t\}_{<t^*} \to M_{t^*}$, and $\{M_t\}_{<t^*} \to Y$ are all present in this DAG, $\{M_t\}_{<t^*}$ plays the role of an *exposure-induced confounder* or *recanting witness*. The presence of such a variable is known to violate one of the key identification assumptions for the NDE/NIE [Pearl, 2001], namely that $Y(a,m) \perp M(a^*) \mid A$ for all m. I refer to this phenomenon as *mediator autoconfounding*.

When the purported mediator process is in fact not a mediator, mediator autoconfounding will not be present, hence under the mediational sharp null [Miles, 2023], the NIE will be correctly identified as zero. However, given the identification challenge under the alternative, the need for a novel indirect effect measure with respect to the full underlying mediator process (whether or not it is actually measured) is apparent. In fact, I would argue that this is what is commonly truly meant when one asks whether the effect of an exposure on an outcome is mediated by some mediator "M". That is, by "M", one is referring to the entire mediator process $\{M\}_{t\in(0,1)}$ rather than at a single time point, M_{t^*}. For the full mediator process $\{M_t\}_{t\in(0,1)}$, I define the *full natural indirect effect* to be $NIE^F \equiv E[Y\{a,\{M_t\}_{(0,1)}(a)\}] - E[Y\{a,\{M_t\}_{(0,1)}(a^*)\}]$. To disambiguate, I will henceforth refer to the traditional NDE/NIE as the *coarsened NDE/NIE*, denoted NDE^C and NIE^C, respectively. When the full mediator process is measured in sufficiently high resolution, then the NIE^F can be identified in terms of the observed data distribution, at least up to approximation error corresponding to the resolution of the measurement. The NIE^F decomposes into the standard NIE as well as other path-specific effects through other parts of the mediator process:

$$
\begin{aligned}
&ATE = NDE^F + NIE^F \\
&\equiv E[Y\{a,\{M_t\}_{(0,\tau)}(a^*)\}] - E[Y\{a^*,\{M_t\}_{(0,\tau)}(a^*)\}] \\
&\quad + E[Y\{a,\{M_t\}_{(0,\tau)}(a)\}] - E[Y\{a,\{M_t\}_{(0,\tau)}(a^*)\}] \\
&= NDE^F + NIE^C + [A \to \{M_t\}_{<t^*} \to Y] \\
&\quad + [A \to \{M_t\}_{<t^*} \to \{M_t\}_{>t^*} \to Y] \\
&\quad + [A \to \{M_t\}_{>t^*} \to Y],
\end{aligned}
$$

where the bracketed terms correspond to path-specific effects with respect to the DAG in Figure 1.

In many cases, it might be reasonable to assume that all effects in this decomposition are in the same direction. When this is the case, we have $|NIE^F| \geq |NIE^C|$ and $\operatorname{sgn}(NIE^F) = \operatorname{sgn}(NIE^C)$, i.e., the NIE^C serves as a lower bound (in magnitude) for the NIE^F. In the absence of further assumptions, the NIE^C is not identified. However, since it likely is identified (by zero) under the mediational sharp null (with respect to the NIE^C), we can at least use the NIE^C to test for the presence and direction of the NIE^F. On the other hand, we cannot say the same for the corresponding NDEs, which will instead be bounded in the opposite direction.

3 DISCUSSION

Based on the findings in this work, I argue that we ought to start reckoning more seriously with the mediator process when discussing mediation. When we only observe the mediator at a single time point, we should critically evaluate whether it is likely that the NIE^C will be identified in practice. To the extent possible, if we are truly interested in mediation, we should try to measure the mediator as frequently as is reasonably possible in order to more directly target the NIE^F.

While some work has been done to consider the mediator as a time-to-event variable [Huang, 2021, Valeri et al., 2021] or as a time-varying covariate [Didelez, 2019], these works have focused on the case in which the mediator happens to fit these particular data types, when in reality, the underlying mediator of interest will most often be a time-varying process of some sort, regardless of whether it is measured as such. When the mediator is a time-to-event variable, survival analysis methods can be employed. Otherwise, for a very frequently and/or irregularly measured mediator, we may need to adopt functional data analysis techniques to estimate nuisance parameters [Lindquist, 2012, Zeng et al., 2023]. Building on this work is an important direction for future research.

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