Mediation analysis for zero-inflated mediators with applications to microbiome data

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Abstract

Zero-inflated data is commonly seen in biomedical research such as microbiome studies and single-cell sequencing studies where zero-valued sequencing reads arise due to technical and/or biological reasons. Mediation analysis approaches for analyzing zero-inflated mediators are still lacking largely because of challenges raised by the zero-inflated data structure: (a) disentangling the mediation effect induced by the point mass at zero is not straightforward; and (b) identifying the observed zero-valued data points that are actually not zero (i.e., false zeros) is difficult. Existing approaches for analyzing microbiome as a high-dimensional mediator can not handle the zero-inflated data structure. In this paper, we developed a novel mediation analysis method under the potential-outcomes framework to fill the research gap. We show that the mediation effect of a zero-inflated mediator can be decomposed into two components that are inherent to the two-part nature of zero-inflated distributions: the first component corresponds to the mediation effect attributable to a unit-change over its positive domain (often counts or continuous values) and the second component corresponds to the mediation effect attributable to discrete jump of the mediator from zero to a non-zero state. With probabilistic models to account for observing zeros, we can also address the challenge with false zeros.
comprehensive simulation study and the applications in two real microbiome studies demonstrate that our approach outperforms current standard mediation analysis approaches.

1 Introduction

Mediation analysis is an important tool to investigate the role of intermediate variables (i.e., mediators) in a causal pathway where the causal effect partially or completely relies on the mediators. For example, people with higher socioeconomic status tend to have longer life expectancy, but this causal pathway may be explained by many possible mediators including access to better health care, fewer stressors, better living environment and so forth. In a mediation analysis, indirect effects (i.e., mediation effects) through one or more mediators can be estimated and tested along with direct effects. This technique was first popularized in psychology and social sciences where traditional linear mediation analysis was proposed, and now is a common tool in many research areas such as epidemiology, environmental health sciences, medicine, randomized trials and psychiatry. Mediation analysis is a powerful approach largely because of its capability to estimate and test the mediation effect that cannot be achieved with typical regression approaches. There are two general types of mediation analysis approaches: potential-outcomes (PO) or counterfactual-outcomes methods [1, 2, 3] and traditional linear mediation analysis methods [4, 5]. The former approach stems from a counterfactual nonparametric function of a causal relationship without relying on linear assumptions and the latter is based on linear regression models. These approaches coincide with each other under linear assumptions. PO approaches are more flexible because they can allow interaction effects of exposure/treatment variable with mediators as well as non-linear effects to be modeled. It is worth noting that assumptions on unmeasured and measured confounders are required to draw causal inference regardless of which type of mediation analysis approach is used. Reviews of mediation analysis approaches and their assumptions can be found in the literature [6, 7, 8].

Although mediation modeling frameworks have been well established, to the best of our knowledge, there have been few studies to address zero-inflated distributions for mediators. In a typical mediation analysis, the total effect of an exposure variable (or treatment or risk factor) can be decomposed into a mediation effect and a direct effect where the mediation effect measures the amount of the total causal effect attributable to change in the mediator caused by the exposure variable and the direct effect measures the causal effect due to change in the exposure variable while keeping the mediator variable constant. When the mediator has a zero-inflated distribution such as a zero-inflated Beta (ZIB) distribution or any other zero-inflated distributions, we show that its mediation effect can be further decomposed into two parts with one part being the mediation effect attributable to the amount of numeric change in the mediator and the other part being the mediation effect attributable to the jump of the mediator from zero to a non-zero state. This phenomenon can be explained by the two-part nature of a zero-inflated distribution. For example, a ZIB distribution is essentially a two-component mixture distribution [9]: one component is a degenerate distribution with probability mass of one at zero, and the other component is a Beta distribution. The mediator changing from zero to a positive value results in the discrete jump from zero to a non-zero state as well as the change in the numerical metric of the mediator and thus mediation effect can be divided accordingly. Both changes have important consequences as we can see in the real study examples later.
where the absence of a microbial taxon and the abundance level of a microbial taxon given its presence are considered. What makes it more complicated is that the observed zero-valued data points could be false zeros meaning that the true values are non-zero but observed as zero due to technical limitations or other reasons. This is similar to a missing data problem and will be addressed here.

Variables with excessive number of zeros are commonly seen in biomedical research studies such as microbiome studies [10], epidemiologic studies [11] and single cell RNA sequencing studies [12]. Many microbiome sequencing reads data have more than 50% observations equal to 0 and it could as high as 80% or more. These zeros are likely a mixture of structural zeros (i.e., true zeros) that represent true absence of microbial taxa and undersampling zeros (i.e., false zeros) that result from lack of assay precision or failure of detection. Existing approaches for analyzing microbiome as a high-dimensional mediator [13] fail to address the zero-inflated data structure. Many epidemiologic research studies frequently generate zero-inflated data as well. For example, when measurement devices have a limit of detection (LOD), values below the LOD are output as below LOD or zero. A typical practice to this problem is to impute zero values with half or square root of half of the LOD value without knowing whether an observed zero is truly zero. In single-cell RNA sequencing studies where transcriptome sequencing is done at single-cell level, zero sequencing reads are very often present due to reasons such as dropout or transient gene expression. The many examples of data sets with zero-inflated data features represents a challenge that needs to be addressed especially in mediation analysis.

To fill the research gap in mediation modeling development, we propose a novel mediation analysis approach under the PO framework to model mediators with zero-inflated distributions. This approach can allow a mixture of true zero-value data points and false zeros due to data collection procedure. Our method is able to decompose the mediation effect into two components that are inherent to zero-inflated mediators: one component is the mediation effect attributable to the numeric change of the mediator on its continuum scale and the other component is the mediation effect attributable to the discrete jump of the mediator from zero to a non-zero state. So the mediation effect is actually the total mediation effect of the two components each of which can be estimated and tested. Our approach has a general framework to accommodate many zero-inflated distributions. For illustration, we consider three typical zero-inflated distributions: zero-inflated beta (ZIB) distribution, zero-inflated log-normal (ZILoN) distribution and zero-inflated Poisson (ZIP) distribution. Since there are no existing mediation approaches targeted for zero-inflated mediators, we use a simulation study to evaluate our approach and show superior performance compared with a current standard PO mediation analysis approach. It is difficult to accommodate zero-inflated mediators under the traditional linear mediation framework because the linear model formulation does not work well with mediators that have two-part distributions.

We introduce model and notation in Section 2. Estimation and inference procedures are provided in Section 3. A simulation study to assess the performance of our model in comparison with standard approaches is presented in Section 4, followed by an application of our model in two real studies in Section 5 and a discussion in Section 6. Additional details and derivations can be found in the Appendix.
2 Model and Notation

For simplicity, we suppress subject index in all notations in this section. Let $M$ denote the mediator with a mixture distribution with the two-part density function given by:

$$f(m; \theta) = \begin{cases} G(\theta), & m = 0 \\ (1 - G(\theta))G(m; \theta), & m > 0 \end{cases}$$

where $\theta$ is the $K$-dimensional parameter vector associated with the distribution, $G(\cdot)$ is a $R^K \rightarrow R$ mapping with $0 < G(\theta) < 1$ being the probability of $M$ taking value of 0 and $G(m; \theta)$ is the conditional probability density (or mass) function of $M$ given that $M$ is positive. Examples include ZIB distribution, ZILoN distribution and ZIP distribution. Let $Y$ denote the outcome variable that has a distribution in exponential family with PDF or PMF given by:

$$f(y; \zeta, \psi) = \exp\left(\frac{y\zeta - a(\zeta) + b(y)}{\psi}\right).$$

By this formulation, we have $E(Y) = a'(\zeta)$ and $\text{var}(Y) = a''(\zeta)\psi$. Let $X$ denote the exposure variable (in a randomized trial $X$ is often the treatment indicator variable). We construct a mediation model consisting of the following equations for a zero-inflated mediator:

$$g(E(Y|M, X)) = \beta_0 + \beta_1 M + \beta_2 1(M>0) + \beta_3 X$$

$$T(\theta) = \nu_0 + \nu_1 X$$

where the first equation is a generalized linear model (GLM), $g(\cdot)$ is a known link function (e.g., identity link for continuous outcomes and logit link for binary outcomes), $1(\cdot)$ is an indicator function, $T: R^K \rightarrow R^K$ is a known one-to-one (possibly nonlinear) transformation of the parameter vector $\theta$, and $\nu_0$ and $\nu_1$ are two $K$-dimensional regression coefficients where $\nu_0$ can be interpreted as the intercept vector and $\nu_1$ as the slope vector. Equation (2) can be considered as a model for the association between $M$ and $X$ since it links the parameter $\theta$ of the mediator $M$ with $X$. Notice that $X$ is a scalar here, but it can be obviously extended to a vector.

Specification of the functions $G(\theta)$ and $T(\theta)$ are likely different for mediators with different distributions. For example, the two part-density function of ZIB distribution is as follows:

$$f(m; \theta) = \begin{cases} G(\theta), & m = 0 \\ (1 - G(\theta)) \frac{m^{\phi-1}(1-m)^{\mu-1}}{B(\mu, (1-\mu)\phi)}, & m > 0 \end{cases}$$

where $\mu$ and $\phi$ are the mean and dispersion parameters respectively of the Beta distribution for the non-zero part \[14, 15\], $\theta = (\mu, \phi, \Delta)^T$ and $G(\theta) = \Delta$. To model the association of the mediator with the exposure $X$, we use $T(\theta) = (\log(\mu/(1-\mu)), \log(\phi), \log(\Delta/(1-\Delta))^T$ in equation (2) for ZIB mediators. Formulation of the models and functions for other scenarios are provided in the Appendix.

2.1 Mechanism for observing zero value of the mediator

In many studies such as microbiome, epidemiology and single-cell sequencing studies, mediator variable might not be detected due to small values or not observed due to
unknown reasons. This phenomenon is similar to missing data problem where the data points are missing and partial information may be available for the missing data (e.g., below limit of detection). Very often zero is used to impute these “missing” data points. For microbiome abundance data, when true abundance cannot be detected due to bad sample quality, quantity or unknown reasons, it is set to be zero. Consequently, there are two types of zeros in the observed abundance data: true abundance of zero (i.e., absence) and abundance that is reported as zero as a consequence of the measurement procedure.

We will use real microbiome studies to illustrate our method in a later section. Let \( M^* \) denote the observed value of the mediator \( M \). When the observed value is positive (i.e., \( M^* > 0 \)), we know that \( M^* = M \). But when \( M^* = 0 \), we don’t know whether \( M \) is truly zero or \( M \) is positive but observed as zero. We consider two mechanisms for observing a zero of the mediator. The first one is given by:

\[
P(M^* = 0|M) = \exp(-\eta M) \quad \text{(3)}
\]

where \( \eta > 0 \) and thus it is a decreasing function of \( M \) such that smaller values of \( M \) are more likely to be observed as zero. Notice that the observed value \( M^* \) is equal to zero with probability of one when \( M = 0 \) which corresponds to the case that \( M \) is truly zero. We refer to this mechanism as ”Probability mechanism” hereafter as every positive data point has a non-zero probability of being observed as a zero. The second mechanism is:

\[
P(M^* = 0|M) = 1_{(M < c)} \quad \text{(4)}
\]

where \( c \) denotes the limit of detection (LOD) which is usually known. Under this mechanism, all true positive values below LOD have an observed value of zero which is commonly seen in epidemiologic studies. We refer to this mechanism as ”LOD mechanism” hereafter. We assume that the probability of observing a zero only depends on \( M \) which implies that it is independent of the outcome \( Y \) conditional on \( M \). It can also be allowed to depend on \( X \) by adding \( X \) to the right-hand side of equations (3) and (4).

### 2.2 Direct and indirect effects

Under the potential-outcomes (PO) framework [7], we can define the natural indirect effect (NIE), natural direct effects (NDE) and controlled direct effect (CDE). Total effect is equal to the summation of NIE and NDE. Let \( M_x \) denote the value of \( M \) if the exposure \( X \) equals \( x \). Let \( Y_{xm} \) denote the value of \( Y \) if \((X, M) = (x, m)\). The average NIE, NDE and CDE for \( X \) changing from \( x_1 \) to \( x_2 \) are defined as:

\[
\begin{align*}
\text{NIE} &= E(Y_{x_2M_{x_2}} - Y_{x_2M_{x_1}}) \\
\text{NDE} &= E(Y_{x_2M_{x_1}} - Y_{x_1M_{x_1}}) \\
\text{CDE} &= E(Y_{x_2m} - Y_{x_1m}) \text{, for a fixed (i.e., controlled) value of } M.
\end{align*}
\]

By plugging the equations (1)-(2) into the above definitions and using Riemann-Stieltjes integration [16], we can obtain the following formulas:

\[
\begin{align*}
\text{NIE} &= E(Y_{x_2M_{x_2}}) - E(Y_{x_2M_{x_1}}) = E(E(Y_{x_2M_{x_2}}|M_{x_2})) - E(E(Y_{x_2M_{x_1}}|M_{x_1})) \\
&= \int_{m \in \Omega} E(Y_{x_2M_{x_2}}|M_{x_2} = m)dF_{M_{x_2}}(m) - \int_{m \in \Omega} E(Y_{x_2M_{x_1}}|M_{x_1} = m)dF_{M_{x_1}}(m) \\
&= \text{NIE}_1 + \text{NIE}_2,
\end{align*}
\]
\[ \text{NIE}_1 = \int_{m \in \Omega \setminus 0} g^{-1}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_2}) dm \\
- \int_{m \in \Omega \setminus 0} g^{-1}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_1}) dm, \]

\[ \text{NIE}_2 = \mathcal{G}(\theta_{x_2}) \left( g^{-1}(\beta_0 + \beta_3 x_2) - \int_{m \in \Omega \setminus 0} g^{-1}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_2}) dm \right) \\
- \mathcal{G}(\theta_{x_1}) \left( g^{-1}(\beta_0 + \beta_3 x_2) - \int_{m \in \Omega \setminus 0} g^{-1}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_1}) dm \right), \]

\[ \text{NDE} = E(Y_{x_2 M_{x_1}} - Y_{x_1 M_{x_1}}) = E(Y_{x_2 M_{x_1}}) - E(Y_{x_1 M_{x_1}}) \\
= \mathcal{G}(\theta_{x_1}) g^{-1}(\beta_0 + \beta_3 x_2) + (1 - \mathcal{G}(\theta_{x_1})) \int_{m \in \Omega \setminus 0} g^{-1}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_1}) dm \\
- \mathcal{G}(\theta_{x_1}) g^{-1}(\beta_0 + \beta_3 x_1) - (1 - \mathcal{G}(\theta_{x_1})) \int_{m \in \Omega \setminus 0} g^{-1}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_1) G(m; \theta_{x_1}) dm \]

\[ \text{CDE} = E(Y_{x_2 M} - Y_{x_1 M}) = E(Y_{x_2 M}) - E(Y_{x_1 M}) \\
= g^{-1}(\beta_0 + \beta_1 m + \beta_2 1_{(m>0)} + \beta_3 x_2) - g^{-1}(\beta_0 + \beta_1 m + \beta_2 1_{(m>0)} + \beta_3 x_1), \]

where \( \Omega \) is the domain of the mediator \( M \), \( F_{M_x}(m) \) denote the CDF of \( M \) conditional on \( X = x \), \( dF_{M_x}(m) \) denote the stieltjes integration \([10]\) with respect to \( F_{M_x}(m) \), \( \theta_x = T^{-1}(\nu_0 + \nu_1 x) \), \( \Omega \setminus 0 \) denote the subset of \( \Omega \) that does not contain 0, and \( \expit(\cdot), g^{-1}(\cdot) \) and \( T^{-1}(\cdot) \) are the inverse functions of logit(\( \cdot \)), \( g(\cdot) \) and \( T(\cdot) \) respectively. NIE, NIE_1, NIE_2, NDE and CDE can be estimated by plugging the parameter estimates into the formulas. Confidence intervals can be obtained using the delta method or resampling methods \([17]\). There are no general closed-form expressions for these quantities. More details of the calculation for indirect and directs effects under different scenarios can be found in the Appendix. NIE_1 can be interpreted as the mediation effect due to the change of the mediator on its numeric scale and NIE_2 can be interpreted as the mediation effect due to the discrete jump of the mediator from zero to non-zero status. This decomposition can be also seen in Figure 1 where there are two indirect causal pathways from \( X \) to \( Y \) through the mediator \( M \). Notice that the decomposition of mediation effect into two parts does not depend on the link function or the form of association of the GLM or the density function of the zero-inflated mediator. So generalization of the decomposition is possible for a broader range of distributions. When the distribution of mediator is not zero-inflated, NIE_2 becomes 0 since \( \mathcal{G}(\theta_{x_2}) \) reduces to 0, and thus the NIE reduces to a usual NIE that can be calculated by standard approaches \([2] [11]\). Notice that it will be very challenging for traditional linear mediation methods to estimate the indirect effect here because of the term \( \beta_2 1_{(M>0)} \) in equation \([1]\) which is not a linear function of the mediator \( M \).

The above formulas use Risk Differences (RD) to quantify indirect and direct effects for binary outcomes \( Y \). A popular alternative measure is Odds Ratio (OR) since OR can be used to estimate relative risk (RR) when the binary outcome is rare or under incidence density sampling \([18]\). The NIE, NDE and CDE can be calculated on the OR scale or
log-OR scale [19] with the following formulas for zero-inflated mediators:

\[
\text{OR}^{\text{NIE}} = \frac{P(Y_{x_2 M_x} = 1)/(1 - P(Y_{x_2 M_x} = 1))}{P(Y_{x_2 M_{x_1}} = 1)/(1 - P(Y_{x_2 M_{x_1}} = 1))} \approx \frac{P(Y_{x_2 M_x} = 1)}{P(Y_{x_2 M_{x_1}} = 1)}
\]

\[
= \frac{\int_{m \in \Omega} P(Y_{x_2 M_x} = 1|M_x = m)dF_{M_x}(m)}{\int_{m \in \Omega} P(Y_{x_2 M_{x_1}} = 1|M_{x_1} = m)dF_{M_{x_1}}(m)}
\]

\[
\mathcal{G}(\theta_{x_2})\expit(\beta_0 + \beta_3 x_2) + (1 - \mathcal{G}(\theta_{x_2})) \int_{m \in \Omega} \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2)G(m; \theta_{x_2})dm
\]

\[
= \mathcal{G}(\theta_{x_1})\expit(\beta_0 + \beta_3 x_2) + (1 - \mathcal{G}(\theta_{x_1})) \int_{m \in \Omega} \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2)G(m; \theta_{x_1})dm.
\]

\[
\text{OR}^{\text{NDE}} = \frac{P(Y_{x_2 M_x} = 1)/(1 - P(Y_{x_2 M_x} = 1))}{P(Y_{x_1 M_{x_1}} = 1)/(1 - P(Y_{x_1 M_{x_1}} = 1))} \approx \frac{P(Y_{x_2 M_x} = 1)}{P(Y_{x_1 M_{x_1}} = 1)}
\]

\[
= \frac{\int_{m \in \Omega} P(Y_{x_2 M_x} = 1|M_x = m)dF_{M_x}(m)}{\int_{m \in \Omega} P(Y_{x_1 M_{x_1}} = 1|M_{x_1} = m)dF_{M_{x_1}}(m)}
\]

\[
\mathcal{G}(\theta_{x_2})\expit(\beta_0 + \beta_3 x_2) + (1 - \mathcal{G}(\theta_{x_2})) \int_{m \in \Omega} \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2)G(m; \theta_{x_2})dm
\]

\[
= \mathcal{G}(\theta_{x_1})\expit(\beta_0 + \beta_3 x_1) + (1 - \mathcal{G}(\theta_{x_1})) \int_{m \in \Omega} \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_1)G(m; \theta_{x_1})dm.
\]

\[
\text{OR}^{\text{CDE}} = \frac{P(Y_{x_2 M} = 1)/(1 - P(Y_{x_2 M} = 1))}{P(Y_{x_1 M} = 1)/(1 - P(Y_{x_1 M} = 1))} = \exp(\beta_0 + \beta_1 m + \beta_2 1_{(m > 0)} + \beta_3 x_2)
\]

\[
= \exp(\beta_0 + \beta_1 m + \beta_2 1_{(m > 0)} + \beta_3 x_1).
\]

\[
3 \text{ Parameter Estimation}
\]

We define a binary variable \(R\) taking values of one or zero to indicate whether \(M^*\) is non-zero or zero. Maximum likelihood estimator (MLE) will be used to estimate the parameters. The variables of observed data for each subject can be denoted by the vector \((Y, R, M^*, X)\) where \(R = 1_{(M^* = 0)}\) and subject index is suppressed. We are not considering any other covariates at this moment for illustration purpose, but the method can be easily extended to cases with covariates included in the equations [1]-[2]. The estimation challenge comes from that \(M\) is not always observable. For some subjects with positive values of \(M\), their \(M^*\) are zero and these are the false zeros. The log-likelihood contribution from those subjects cannot be directly calculated. However, given we know the probability of observing a zero in equation [3] or [4], we can still obtain their log-likelihood contributions by integrating the joint density function over all possible values of \(M\) using Riemann-Stieltjes integration [16]. Let \((y_i, r_i, m_i^*, x_i)\) denote the observed data values for the \(i\)th subject in the study and \(m_i\) denote the true value of the mediator. We use \(i\) as subject index hereafter throughout the paper. The subjects are divided into two groups by whether \(M^*\) is non-zero or zero. The first group consists of subjects whose observed value of \(m_i\) is non-zero (i.e., \(m_i^* \neq 0\)). In this group we have \(m_i^* = m_i\) and the
log-likelihood contribution from the $i$th subject can be calculated as:

$$l_i^1 = \log(f(y_i, r_i|m_i^*, x_i)f(m_i^*|x_i)) = \log(f(y_i|m_i^*, x_i)f(r_i|m_i^*, x_i)f(m_i^*|x_i))$$

$$= \log(f(y_i|m_i^*, x_i)) + \log(f(r_i|m_i^*)) + \log(f(m_i^*|x_i))$$

$$= \log(f(y_i; \zeta, \psi)) + \log(1 - P(M_i^* = 0|M_i = m_i^*)) + \log((1 - G(\theta_{x_i}))G(m_i^*; \theta_{x_i})), \quad (5)$$

where $y_i$, $r_i$, $m_i^*$ and $x_i$ are the observed values of $Y$, $R$, $M^*$ and $X$ respectively for the $i$th subject, $f(\cdot|m_i^*, x_i)$, $f(\cdot|m_i^*, x_i)$ and $f(\cdot|x_i)$ are the (conditional) density (or probability mass function) for $Y$, $R$ and $M$ respectively. Closed-form expressions for specific cases are available in the Appendix. Let $F(m|x)$ denote the (conditional) cumulative distribution function for $M$. The second group consists of subjects whose observed $m_i$ are 0 (ie, $m_i^* = 0$) and their log-likelihood contribution can be calculated as:

$$l_i^2 = \log(f(y_i, r_i, m_i^*|x_i)) = \log\left(\int_{m \in \Omega} f(y_i|m, x_i)f(r_i|m)dF(m|x_i)\right)$$

$$= \log\left(G(\theta_{x_i})f(y_i; \zeta, \psi) + (1 - G(\theta_{x_i})) \int_{m \in \Omega \setminus 0} f(y_i|m, x_i)P(M_i^* = 0|M_i = m))G(m; \theta_{x_i})dm,\right)$$

where the integral in the last row can be approximated by tanh-sinh quadrature \cite{20}. 

Taken together, we have the complete log-likelihood function given by

$$l = \sum_{i \in \text{group 1}} l_i^1 + \sum_{i \in \text{group 2}} l_i^2. \quad (6)$$

In general, there is no general closed-form expression for $l$ due to the integration. More details of calculating $l$ under different scenarios are given in the Appendix. We obtain MLE of the parameters by maximizing the above complete log-likelihood function. With the parameter estimates, we will be able to calculate NIE, NIE1, NIE2, NDE and CDE and their confidence intervals using the delta method or resampling methods \cite{17}.

### 4 Simulation

Extensive simulations were carried out to demonstrate the performance of the proposed model for three commonly seen zero-inflated distributions of the mediator $M$: ZIB, ZILoN and ZIP. The mediation model with ZIB mediators can be directly applied to microbiome relative abundance (RA) data since RA data can be modeled with ZIB distributions \cite{21}. We studied both continuous and binary outcomes $Y$ in the simulation. The independent variable $X$ was generated using the standard normal distribution. The true parameter values used in the data generation can be found in Tables \cite{16} for different settings. To generate zero-valued data points for the mediator $M$, both the Probability mechanism indicated by equation (3) and the LOD mechanism indicated by equation (4) for observing zero-valued data points of the mediator were considered in the data generation. We compared our approach with a causal mediation analysis approach developed in Imai, Keele and Tingley \cite{2} (IKT approach hereafter) which is a PO approach and can be implemented in R using the package mediation \cite{22}. The Marginal Structural Models method developed in VanderWeele \cite{11} is also a PO approach with a very similar definition of indirect effect. For each of the settings in the simulation study, we generated 100
random samples and 300 subjects in each sample. Explicit model equations and formulas for calculating the NIE, NIE\(_1\), NIE\(_2\), NDE and CDE in each setting are provided in the Appendix. Model performance was evaluated by estimation bias, standard error, coverage probability (CP) of 95% confidence intervals (CI) of the estimators for parameters and the indirect and direct effects.

4.1 Microbiome relative abundance (RA) as mediator variables

We analyzed microbial taxa RA as mediators with ZIB distributions together with a continuous outcome in one of the simulation settings where the mediation model equations are given by (7)-(10). Data were generated based on those model equations and using the true parameter values in Table 1. The Probability mechanism in equation (3) was used to generate the false zeros and the proportion of false zeros can be adjusted by varying the value of parameter \(\eta\). To mimic the real data sparsity level in microbiome studies, about 50% of the data points in the generated microbiome data sets are zero among which about half are true zeros and the other half are false zeros. Estimates for all parameters including \(\eta\) and the indirect and direct effects are presented in the left panel of Table 1. Our approach has desired performance in terms of the model performance indices. There are virtually no bias of the estimators and the CP’s of 95% CI’s are close to 95%. When compared with the IKT approach [2], our method has much better bias and CP for NIE. The IKT approach provides severely biased estimate of NIE and the CP for NIE is significantly underestimated (the CP of NIE is 0%). The advantage of our approach comes from the fact that our model takes into account the zero-inflated structure of the mediator as well as the mechanisms for observing false zero values of the mediator. In addition, our approach can also provide estimates and 95% CI’s for NIE\(_1\) and NIE\(_2\) that represent the mediation effect through the change on the numeric scale and the discrete jump of the mediator respectively, whereas the IKT approach does not provide the decomposition of mediation effect. For ZIB mediators and binary outcomes, the mediation model equations are given in (12)-(15) and the data were generated in a similar way. Again the Probability mechanism in equation (3) was used to generate false zeros. The simulation results (See left panel of Table 2) have similar pattern to that with continuous outcomes.

We also checked the model performance for ZIB mediators under the LOD mechanism for observing false zeros where the LOD is assumed to be known. Equation (4) was used to generate the false zeros that account for half of all zeros. We are aware of that the LOD value for microbiome RA data is usually unknown or does not make sense in practice. So we suggest using the Probability mechanism to account for false zeros in real data sets as described above to analyze microbial RA data. This simulation is to demonstrate the model performance and the simulation results are provided on the right panels of Tables 1 and 2. Again our approach has reasonable performance on all performance indices and show superior performance than IKT approach.

4.2 ZILoN and ZIP mediators

ZILoN and ZIP mediators were studied as well in the simulation with continuous and binary outcomes under the Probability mechanism and the LOD mechanism for observing false zeros (see Tables 3-6). The corresponding model equations and formulas are provided in the Appendix. About 50% of all data points were zeros in each generated data set.
and half of all zeros are false zeros. Similar to the results for ZIB mediators presented above, our approach was consistently better across all situations and outperformed the IKT approach by a big margin in most situations. For instance, the CP for NIE of our approach is 93% under the setting with ZIP mediators, the Probability mechanism for observing zeros and binary outcomes (See left panel in Table 6) whereas IKT approach has only 0% CP due to its huge estimation bias. This is also the case under the LOD mechanism for observing zeros (See right panel in Table 6).

5 Real data applications

5.1 New Hampshire Birth Cohort Study (NHBCS)

The NHBCS is an NIH-funded ongoing prospective epidemiological study to investigate the health impacts of environmental exposures with a focus on arsenic exposure in pregnant women and their children [23]. Pregnant women were recruited at about 24 to 28 weeks of gestational age and both mothers and babies are followed up after birth. We applied our approach in the NHBCS study to examine the mediation effect of gut microbiome in the causal pathway from maternal arsenic exposure to infant’s health outcomes during the first year of life. In our analysis, the total in-utero arsenic level [24] was the exposure variable $X$, gut microbiome of infants at 6 weeks of age was the mediator $M$ and the outcome $Y$ is cough treated with a prescribed medicine between 8 and 12 months of age. Here $X$ is a continuous variable and $Y$ is a binary variable coded as 1/0 indicating yes/no. The gut microbiome data was measured in DNA extracted from infant stool samples using 16S rRNA sequencing [25, 26]. RA of a microbial taxon was calculated by summing up the RA of OTUs in the OTU table that were assigned to that taxon. After quality control and data cleaning, there were 67 subjects and 176 genera available in the data set. 54% of the microbiome data points were zero. The Probability mechanism in equation (3) for observing zero was assumed. Relative abundance (RA) of each genus was analyzed as a mediator variable using the ZIB distribution. Our model framework does not require the microbiome data be analyzed at the genus level, it can be flexible and at any other level (e.g., species level). We estimated all mediation effects (i.e., NIE$_1$, NIE$_2$, NIE) and their 95% confidence intervals (CI) for the exposure variable increasing from 0 to 1 meaning $x_1 = 0$ and $x_2 = 1$. Notice that $x_1$ and $x_2$ can take other values as needed depending on the interest of investigators. We used the FDR approach [27] for multiple-testing adjustment and the 95% CI were calculated before the adjustment. The results are presented in Table 7 in comparison with the IKT approach. We found 2 genera (Sphingomonadales and Coprobacillus) that are statistically significantly mediating the effect of in-utero arsenic on the cough outcome. The results are also shown in a phylogenetic tree in Figure 2. The mediation effects come from NIE$_2$ for both genera which means that the presence of the genera mediate the effect but the changes in RA level do not appear to influence the risk. On average, the mediation effects of Sphingomonadales and Coprobacillus decrease the risk of cough by 3% and 8% respectively. Sphingomonadales and its family Sphingomonadaceae have both been linked to airway-related diseases in the literature [28, 29, 30]. Coprobacillus belongs to the family of Erysipelotrichaceae which has also been linked to chronic respiratory disease [31]. The IKT approach did not find any significant mediation effect of the microbial taxa and it failed to generate result for one of the genera that were found to be significant by our approach.
5.2 VSL#3 mouse model

VSL#3 is a commercially available probiotic cocktail (Sigma-Tau Pharmaceuticals, Inc.) of eight strains of lactic acid-producing bacteria: *Lactobacillus plantarum*, *Lactobacillus delbrueckii subsp*. *Bulgaricus*, *Lactobacillus paracasei*, *Lactobacillus acidophilus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, and *Streptococcus salivarius subsp*. Orally administered VSL#3 has shown success in ameliorating symptoms and reducing inflammation in human pouchitis [32] and ulcerative colitis [33]. Preventive VSL#3 administration can also attenuate colitis in Il10-/- mice [34] and ileitis in SAMP1/YitFc mice [35]. So when used as a preventative strategy, it has the capability to prevent inflammation and carcinogenesis. In a mouse model, Arthur et al. [36] studied the ability of probiotic cocktail VSL#3 to alter the colonic microbiota and decrease inflammation-associated colorectal cancer when administered as interventional therapy after the onset of inflammation. The study duration was 24 weeks. In this study, there were totally 24 mice of which 10 were treated with VSL#3 and 14 served as control. Gut microbiome data were collected from stools at the end of the study with 16S rRNA sequencing. We obtained the sequencing data for Arthur et al. [36] and generated open reference OTUs using the Quantitative Insights into Microbial Ecology (QIIME) [37] version 1.9.1 at 97% similarity level using the Greengenes 97% reference dataset (release 13.8). Chimeric sequences were detected and removed using QIIME. OTUs that had 0.005% of the total number of sequences were excluded according to Bokulich and colleagues [38]. Taxonomic assignment was done using the RDP (ribosomal database project) classifier [39] through QIIME with confidence set to 50%. There were 426 OTUs in total in the data sets after quality control and data cleaning. 40% of the OTU RA data points were zero.

RA of each OTU was analyzed as a mediator variable using the ZIB distribution. The Probability mechanism in equation (3) was assumed for observing zero-valued microbiome data points. The outcome variable in our analysis was dysplasia score (the higher the worse), a continuous variable measuring the abnormality of cell growth. The treatment variable is coded as 1/0 indicating VSL#3/control. Analysis results are presented in Table 8. Again, the FDR approach was used for adjusting for multiple testing and the 95% CI were calculated before adjustment. Four OTUs were found to be significantly mediating the treatment effects. One of the four OTUs was assigned to the order Bacillales, two were assigned to genera (*Clostridium* and *Ruminococcus*) and one was assigned to kingdom Bacteria. The results are also shown in a phylogenetic tree in Figure 3. All the significant mediation effects come from NIE₂ implying that only the mediation effects through the discrete change in M from zero to non-zero are significantly contributing to the total mediation effects. The mediation effect sizes are -1.75, -1.37, -1.37 and -1.38 respectively for the four OTUs meaning that the dysplasia score are reduced by 1.75, 1.37, 1.37 and 1.38 respectively due to the mediation effects. Our analysis found more OTUs mediating the effect of VSL#3 than Arthur et al. [36] where the researchers employed traditional linear mediation analysis approach and found that the loss of an OTU from genus *Clostridium* contributed to increased tumorigenesis (at significance level of 0.10) which is consistent with one of our findings. The genus *Ruminococcus* and order Bacillales found by our approach have also been reported to be associated with colorectal cancer in the literature [40, 41]. The IKT approach did not find any significant mediation effects in this data set.
6 Discussion

We developed an innovative mediation modeling approach under the PO framework to analyze mediators that have zero-inflated distributions which are commonly seen in biomedical research studies. We showed that mediation effect for zero-inflated mediators can be decomposed into two components of which the first is due to the change in mediator over its positive domain (often counts or continuous values) and the second is due to the discrete jump from zero to non-zero status. These two components have different interpretations and are equally important for investigating causal mechanisms. Although the derivation of the decomposition were done under a generalized linear model (GLM) for the outcome variable, it can be easily extended to cases beyond GLM. When the point mass \( G(\theta) \) is zero for the mediator (i.e., the distribution is not zero-inflated), the model reduces to a usual mediation analysis model. Multiple commonly seen zero-inflated distributions for the mediator were considered in this paper for illustration purposes although this is a general framework for mediators with zero-inflated distributions. This tool will be useful for researchers to evaluate the mediation effects of zero-inflated mediators and disentangle causal pathways that are scientifically important. Hence it can play an important role in translating research findings into medical practice. R scripts for implementing the method is available upon request.

This paper considered \( X \) as a univariate variable for illustration purpose and did not include covariates as potential confounders in the models. It is straightforward to adjust for a set of covariates using our approach. Let \( C \) denote a vector of covariates or potential confounders. Then the NIE and NDE can be calculated at a specific value, \( c \), of \( C \) as \( \text{NIE} = E(Y_{x2}M_{x2} - Y_{x2}M_{x1} | C = c) \), \( \text{NDE} = E(Y_{x2}M_{x1} - Y_{x1}M_{x1} | C = c) \) and \( \text{CDE} = E(Y_{x2m} - Y_{x1m} | C = c) \). Value \( c \) can be taken as the mean value of the covariates similar to how least squares mean is calculated in regression models \[42\]. Confidence intervals can be obtained using delta method or resampling methods. Decomposition of NIE follows the same procedure as shown in Section 2.2.

Several extensions of our approach in future research are worth noting. As the derivation of the decomposition for mediation effect does not depend on the specific form of the association between \( Y \) and \( M \) and \( X \), nonparametric/semi-parametric functions can be used to accommodate broader nonlinear relationships. For high-dimensional mediators, our method can analyze the mediators one by one and employ the FDR method \[27\] to adjust for multiple testing. Although our approach can handle compositional structure of microbiome data by allowing zero-inflated Beta distributions for mediators, the correlation due to hierarchical structure of phylogenetic tree is not utilized when the microbial taxa are analyzed one by one. A natural extension of our approach would be to include all the mediators in a single model and use regularization approaches \[43, 44\] to select mediators for the model. Four assumptions on unmeasured and measured confounders \[1\] are required to make causal inference for mediation analysis. Sensitivity analysis \[45, 46\] can be useful to check the robustness of model performance with respect to validation of the assumptions. Existing sensitivity analysis procedures can be adapted in our setting for developing a sensitivity analysis method for our approach. Misspecification of the mechanisms for observing zero-valued data points could have an impact on the model performance. As mentioned earlier, this is similar to missing data where partial information is available on the missing data. It can be considered as missing not at random (MNAR) \[47\] because the probability of a data point being observed as zero depends on its true value. Although the Probability mechanism and LOD mechanism for observing
zeros may not be perfect to account for MNAR, it can, to a large extent, alleviate the burden of not accounting for false zeros in the data at all. A future project has been planned to study the robustness of our model with respect to the mechanism for observing zeros using sensitivity analysis techniques.

References

[1] Tyler J. VanderWeele. Marginal structural models for the estimation of direct and indirect effects. *Epidemiology*, 20:18–26, 2009.

[2] Kosuke Imai, Luke Keele, and Dustin Tingley. A general approach to causal mediation analysis. *Psychological Methods*, 15:309–334, 2010.

[3] Tyler J. VanderWeele. *Explanation in Causal Inference: Methods for Mediation and Interaction*. New York: Oxford Univ. Press, 2015.

[4] Reuben M. Baron and David A Kenny. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic and statistical considerations. *Journal of Personality and Social Psychology*, 51:1173–1182, 1986.

[5] David P. MacKinnon. *Introduction to statistical mediation analysis*. New York: Erlbaum, 2008.

[6] David P MacKinnon, Amanda J Fairchild, and Matthew S Fritz. Mediation analysis. *Annual review of psychology*, 58:593–614, 2007.

[7] Tyler J. VanderWeele. Mediation analysis: A practitioner’s guide. *Annu Rev Public Health*, 37:17–32, 2016.

[8] Theis Lange, Kim Wadt Hansen, Rikke Srensen, and Sren Galatius. Applied mediation analyses: a review and tutorial. *Epidemiology and health*, 39:e2017035, 2017.

[9] M. L. Dalrymple, I. L. Hudson, and R. P. K. Ford. Finite mixture, zero-inflated Poisson and hurdle models with application to SIDS. *Computational Statistics & Data Analysis*, 41(3-4):491–504, 2003.

[10] Hongzhe Li. Statistical and computational methods in microbiome and metagenomics. *Handbook in Statistical Genomics*, 2018.

[11] Brian W Whitcomb and Enrique F Schisterman. Assays with lower detection limits: implications for epidemiological investigations. *Paediatric and perinatal epidemiology*, 22:597–602, November 2008.

[12] Byungjin Hwang, Ji Hyun Lee, and Duhee Bang. Single-cell rna sequencing technologies and bioinformatics pipelines. *Experimental and molecular medicine*, 50:96, August 2018.

[13] Michael B. Sohn and Hongzhe Li. Compositional mediation analysis for microbiome studies. *The Annals of Applied Statistics*, 13(1):661–681, 2019.
[14] Silvia Ferrari and Francisco Cribari-Neto. Beta regression for modelling rates and proportions. *Journal of Applied Statistics*, 31:799–815, 2004.

[15] Francisco Cribari-Neto and Achim Zeileis. Beta regression in R. *Journal of Statistical Software*, 34:24848, 2010.

[16] H. J. Terhorst. On stieltjes integration in euclidean-space. *Journal of Mathematical Analysis and Applications*, 114(1):57–74, 1986.

[17] B Efron and R Tibshirani. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Statistical Science*, 1(1):54–75, 1986.

[18] D B Richardson. An incidence density sampling program for nested case-control analyses. *Occupational and Environmental Medicine*, 61:e59, December 2004.

[19] Tyler J VanderWeele and Stijn Vansteelandt. Odds ratios for mediation analysis for a dichotomous outcome. *American Journal of Epidemiology*, 172:1339–1348, December 2010.

[20] David H. Bailey, Karthik Jeyabalan, and Xiaoye S. Li. A comparison of three high-precision quadrature schemes. *Experimental Mathematics*, 14:317–329, 2005.

[21] Eric Z Chen and Hongzhe Li. A two-part mixed-effects model for analyzing longitudinal microbiome compositional data. *Bioinformatics (Oxford, England)*, 32:2611–2617, September 2016.

[22] Dustin Tingley, Teppei Yamamoto, Kentaro Hirose, Luke Keele, and Kosuke Imai. mediation: R package for causal mediation analysis. https://cran.r-project.org/web/packages/mediation/vignettes/mediation.pdf, 2017.

[23] S Farzan, S Korrick, Z Li, R Enelow, A Gandolfi, J Madan, K Nadeau, and M Karagas. In utero arsenic exposure and infant infection in a united states cohort: A prospective study. *Environmental Research*, 126:24–30, 2013.

[24] Kari C Nadeau, Zhigang Li, Shohreh Farzan, Devin Koestler, David Robbins, Dennis Liang Fei, Meena Malipatlolla, Holden Maecker, Richard Enelow, Susan Korrick, et al. In utero arsenic exposure and fetal immune repertoire in a us pregnancy cohort. *Clinical Immunology*, 155(2):188–197, 2014.

[25] Juliette C Madan, Anne G Hoen, Sara N Lundgren, Shohreh F Farzan, Kathryn L Cottingham, Hilary G Morrison, Mitchell L Sogin, Hongzhe Li, Jason H Moore, and Margaret R Karagas. Association of cesarean delivery and formula supplementation with the intestinal microbiome of 6-week-old infants. *JAMA Pediatrics*, 170:212–219, March 2016.

[26] Zhigang Li, Katherine Lee, Margaret R. Karagas, Juliette C. Madan, Anne G. Hoen, A. James O’ Malley, and Hongzhe Li. Conditional regression based on a multivariate zero-inflated logistik-normal model for microbiome relative abundance data. *Stat Biosci*, pages 1–22, jul 2018.

[27] Y. Benjamini and Y. Hochberg. Controlling the false discovery rate: A Practical and powerful approach to multiple testing. *J. Roy. Statist. Soc.*, 57:289–300, 1995.
[28] Christopher J Van Der Gast, Leah Cuthbertson, Geraint B Rogers, Christopher Pope, Robyn L Marsh, Gregory J Redding, Kenneth D Bruce, Anne B Chang, and Lucas R Hoffman. Three clinically distinct chronic pediatric airway infections share a common core microbiota. *Annals of the American Thoracic Society*, 11(7):1039–1048, 2014.

[29] Yvonne J Huang, Sanjay Sethi, Timothy Murphy, Snehal Nariya, Homer A Boushey, and Susan V Lynch. Airway microbiome dynamics in exacerbations of chronic obstructive pulmonary disease. *Journal of clinical microbiology*, 52(8):2813–2823, 2014.

[30] Kian Fan Chung. Airway microbial dysbiosis in asthmatic patients: A target for prevention and treatment? *The Journal of allergy and clinical immunology*, 139:1071–1081, April 2017.

[31] Yvonne J Huang and Susan V Lynch. The emerging relationship between the airway microbiota and chronic respiratory disease: clinical implications. *Expert review of respiratory medicine*, 5:809–821, December 2011.

[32] Paolo Gionchetti, Fernando Rizzello, Alessandro Venturi, Patrizia Brigidi, Diego Matteuzzi, Gabriele Bazzocchi, Gilberto Poggioi, Mario Miglioli, and Massimo Campieri. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology*, 119(2):305–309, 2000.

[33] Ajit Sood, Vandana Midha, Govind K Makharia, Vineet Ahuja, Dinesh Singal, Pooja Goswami, and Rakesh K Tandon. The probiotic preparation, vsl#3 induces remission in patients with mild-to-moderately active ulcerative colitis. *Clinical Gastroenterology and Hepatology*, 7(11):1202–1209, 2009.

[34] Karen Madsen, Anthony Cornish, Paul Soper, Conor McKaigney, Humberto Ji-jon, Christine Yachimec, Jason Doyle, Lawrence Jewell, and Claudio De Simone. Probiotic bacteria enhance murine and human intestinal epithelial barrier function. *Gastroenterology*, 121(3):580–591, 2001.

[35] Cristiano Pagnini, Rubina Saeed, Giorgos Bamias, Kristen O Arseneau, Theresa T Pizarro, and Fabio Cominelli. Probiotics promote gut health through stimulation of epithelial innate immunity. *Proceedings of the national academy of sciences*, 107(1):454–459, 2010.

[36] Janelle C Arthur, Raad Z Gharaibeh, Joshua M Uronis, Ernesto Perez-Chanona, Wei Sha, Sarah Tomkovich, Marcus Muhlauer, Anthony A Fodor, and Christian Jobin. Vsl# 3 probiotic modifies mucosal microbial composition but does not reduce colitis-associated colorectal cancer. *Scientific reports*, 3:2868, 2013.

[37] J Gregory Caporaso, Justin Kuczynski, Jesse Stombaugh, Kyle Bittinger, Frederic D Bushman, Elizabeth K Costello, Noah Fierer, Antonio Gonzalez Pena, Julia K Goodrich, Jeffrey I Gordon, et al. Qiime allows analysis of high-throughput community sequencing data. *Nature methods*, 7(5):335, 2010.

[38] Nicholas A Bokulich, Sathish Subramanian, Jeremiah J Faith, Dirk Gevers, Jeffrey I Gordon, Rob Knight, David A Mills, and J Gregory Caporaso. Quality-filtering
vastly improves diversity estimates from illumina amplicon sequencing. *Nature methods*, 10(1):57, 2013.

[39] Qiong Wang, George M Garrity, James M Tiedje, and James R Cole. Naive bayesian classifier for rapid assignment of rRNA sequences into the new bacterial taxonomy. *Appl. Environ. Microbiol.*, 73(16):5261–5267, 2007.

[40] Ccily Lucas, Nicolas Barnich, and Hang Thi Thu Nguyen. Microbiota, inflammation and colorectal cancer. *International journal of molecular sciences*, 18, June 2017.

[41] Ahmed O Alomair, Ibrahim Masoodi, Essam J Alyamani, Abed A Allehibi, Adel N Qutub, Khalid N Alsayari, Musaad A Altammami, and Ali S Alshanqeeti. Colonic mucosal microbiota in colorectal cancer: A single-center metagenomic study in saudi arabia. *Gastroenterology research and practice*, 2018:5284754, 2018.

[42] D. Gianola. Least-squares means vs population marginal means. *American Statistician*, 36(1):65–66, 1982.

[43] Cun-Hui Zhang. Nearly unbiased variable selection under minimax concave penalty. *The Annals of Statistics*, 38(2):894–942, 2010.

[44] Robert Tibshirani. Regression shrinkage and selection via the lasso: a retrospective. *Journal of the Royal Statistical Society. Series B. Statistical Methodology*, 73(3):273–282, 2011.

[45] Tyler J VanderWeele and Yasutaka Chiba. Sensitivity analysis for direct and indirect effects in the presence of exposure-induced mediator-outcome confounders. *Epidemiology, biostatistics, and public health*, 11, 2014.

[46] Kosuke Imai, Luke Keele, and Tepps Yamamoto. Identification, inference and sensitivity analysis for causal mediation effects. *Statistical Science*, 25(1):51–71, 2010.

[47] Roderick JA Little and Donald B Rubin. *Statistical analysis with missing data*, volume 333. John Wiley & Sons, 2014.

7 Appendix

7.1 Model for ZIB mediators and continuous outcomes

For a ZIB mediator $M$, its two-part density can be written as the following:

$$f(m; \theta) = \begin{cases} G(\theta), & m = 0 \\ (1 - G(\theta))G(m; \theta), & m > 0 \end{cases}$$

where $\theta = (\mu, \phi, \Delta)$, $G(\theta) = \Delta$ and

$$G(m; \theta) = \frac{m^{\mu-1}(1-m)^{(1-\mu)\phi-1}}{B(\mu\phi, (1-\mu)\phi)}, \quad m \in (0, 1), 1 > \mu > 0, \phi > 0.$$

Here we use the mean and dispersion parameterization for the Beta density function $G(m; \theta)$ [14, 15]. The transformation function and vectors in equation [2] are given by:
The mediation model consists of the following equations:

\[ T(\theta) = (\log(\mu/(1-\mu)), \log(\sigma), \log(\Delta/(1-\Delta)))^T, \quad \nu_0 = (\alpha_0, \xi_0, \gamma_0)^T \quad \text{and} \quad \nu_1 = (\alpha_1, \xi_1, \gamma_1)^T. \]

We use identity link for \( g(\cdot) \) in equation (1) since \( Y \) is a continuous outcome, and thus the mediation model consists of the following equations:

\[
Y = \beta_0 + \beta_1 M + \beta_2 1_{(M>0)} + \beta_3 X + \epsilon, \quad (7)
\]

\[
\log \left( \frac{\mu}{1-\mu} \right) = \alpha_0 + \alpha_1 X, \quad (8)
\]

\[
\log(\phi) = \xi_0 + \xi_1 X, \quad (9)
\]

\[
\log \left( \frac{\Delta}{1-\Delta} \right) = \gamma_0 + \gamma_1 X, \quad (10)
\]

The formulas for NIE, NDE and CDE are

\[
\text{NIE} = E(Y_{x_2,m_{x_2}} - Y_{x_2,m_{x_1}}) \\
= E(\beta_1 (M_{x_2} - M_{x_1}) + \beta_2 (1_{(M_{x_2} > 0)} - 1_{(M_{x_1} > 0)})) \\
= \beta_1 E(M_{x_2}) - E(M_{x_1}) + \beta_2 (E(1_{(M_{x_2} > 0)}) - E(1_{(M_{x_1} > 0)})) \\
= \text{NIE}_1 + \text{NIE}_2,
\]

\[
\text{NIE}_1 = \beta_1 \left( \expit(\alpha_0 + \alpha_1 x_2) - \expit(\alpha_0 + \alpha_1 x_1) \right)
\]

\[
\text{NIE}_2 = \beta_2 \left( \expit(\gamma_0 + \gamma_1 x_2) - \expit(\gamma_0 + \gamma_1 x_1) \right)
\]

\[
- \beta_1 \left( \expit(\gamma_0 + \gamma_1 x_2) \expit(\alpha_0 + \alpha_1 x_2) - \expit(\gamma_0 + \gamma_1 x_1) \expit(\alpha_0 + \alpha_1 x_1) \right)
\]

\[
\text{NDE} = E(Y_{x_2,m_{x_1}} - Y_{x_1,m_{x_1}}) = \beta_3(x_2 - x_1),
\]

\[
\text{CDE} = E(Y_{x_2,m} - Y_{x_1,m}) = \beta_3(x_2 - x_1).
\]

### 7.1.1 Log-likelihood function under the Probability mechanism with equation (3)

Let \((y_i, r_i, m^*_i, x_i)\) denote the observed data for the \(i\)th subject. The log-likelihood contribution from the first group can be calculated as:

\[
l'_i = \log(f(y_i, r_i|m^*_i, x_i)) = \log(f(y_i|m^*_i, x_i)) f(r_i|m^*_i, x_i) f(m^*_i|x_i)) \]

\[
= \log(f(y_i|m^*_i, x_i)) + \log(f(r_i|m^*_i)) + \log(f(m^*_i|x_i)) \]

\[
= - \log(\delta) - \frac{(y_i - \beta_0 - \beta_1m^*_i - \beta_2 - \beta_3x_i)^2}{2\delta^2} + \log(1 - \exp(-\eta^2m^*_i)) \]

\[
+ \log(1 - \Delta_i) - \log \left( B(\mu_i \phi_i, (1-\mu_i)\phi_i) \right) \]

\[
+ (\mu_i \phi_i - 1) \log(m^*_i) + ((1 - \mu_i)\phi_i - 1) \log(1 - m^*_i) + \text{cons}, \quad (11)
\]

where \(\Delta_i = \expit(\gamma_0 + \gamma_1 x_i)\), \(\mu_i = \expit(\alpha_0 + \alpha_1 x_i)\) and \(\phi_i = \expit(\xi_0 + \xi_1 x_i)\). The log-likelihood contribution from the second group can be calculated as:

\[
l''_i = \log(f(y_i, r_i, m^*_i|x_i)) = \log \left( \int_0^1 f(y_i, r_i|m, x_i) dF(m|x_i) \right) \]

\[
= \log \left( \int_0^1 f(y_i|m, x_i) f(r_i|m) dF(m|x_i) \right)
\]

17
The log-likelihood contribution from the second group can be calculated as:

\[ l_2 = \log \left( \frac{\Delta_i}{\sqrt{2\pi\delta^2}} \exp \left( -\frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) \right) + \int_0^c f(y_i|m, x_i)(1 - \Delta_i) \frac{m^\mu\phi^{-1}(1 - m)(1 - \mu)^{\phi-1} \exp(-\eta^2 m)}{B(\mu, \phi_i, (1 - \mu_i)\phi_i)} \, dm \]

\[ = -\log(\delta) + \log \left( \Delta_i \exp \left( -\frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) \right) + \frac{1 - \Delta_i}{B(\mu, \phi_i, (1 - \mu_i)\phi_i)} \int_0^c h_i(m) \, dm \]

+ \text{cons},

where

\[ h_i(m) = m^\mu\phi^{-1}(1 - m)(1 - \mu)^{\phi-1} \exp \left( -\frac{(y_i - \beta_0 - \beta_1 m - \beta_2 - \beta_3 x_i)^2}{2\delta^2} - \eta^2 m \right). \]

Taken together, the complete log-likelihood function can be calculated as in equation \( \text{(6)} \).

### 7.1.2 Log-likelihood function under the LOD mechanism with equation (4)

The log-likelihood contribution from the first group can be calculated as:

\[ l_1 = \log(f(y_i, r_i|m^*_i, x_i)f(m^*_i|x_i)) = \log(f(y_i|m^*_i, x_i)f(r_i|m^*_i, x_i)f(m^*_i|x_i)) \]
\[ = \log(f(y_i|m^*_i, x_i)) + \log(f(r_i|m^*_i)) + \log(f(m^*_i|x_i)) \]
\[ = -\log(\delta) - \frac{(y_i - \beta_0 - \beta_1 m^*_i - \beta_2 - \beta_3 x_i)^2}{2\delta^2} \]
\[ + \log(1 - \Delta_i) - \log \left( B(\mu, \phi_i, (1 - \mu_i)\phi_i) \right) \]
\[ + (\mu_i\phi_i - 1) \log (m_i^*) + ((1 - \mu_i)\phi_i - 1) \log (1 - m_i^*) + \text{cons}. \]

The log-likelihood contribution from the second group can be calculated as:

\[ l_2 = \log(f(y_i, r_i, m^*_i|x_i)) = \log \left( \int_0^c f(y_i, r_i|m, x_i)dF(m|x_i) \right) \]
\[ = \log \left( \int_0^c f(y_i|m, x_i)f(r_i|m)dF(m|x_i) \right) \]
\[ = \log \left( \frac{\Delta_i}{\sqrt{2\pi\delta^2}} \exp \left( -\frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) \right) \]
\[ + \int_0^c f(y_i|m, x_i)(1 - \Delta_i) \frac{m^\mu\phi^{-1}(1 - m)(1 - \mu)^{\phi-1} \exp(-\eta^2 m)}{B(\mu, \phi_i, (1 - \mu_i)\phi_i)} \, dm \]
\[ = -\log(\delta) + \log \left( \Delta_i \exp \left( -\frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) \right) + \frac{1 - \Delta_i}{B(\mu, \phi_i, (1 - \mu_i)\phi_i)} \int_0^c h_i(m) \, dm \]

+ \text{cons},
Where \( c \in (0, 1) \) and

\[
h_i(m) = m^{\mu_i \phi_i - 1} (1 - m)^{(1 - \mu_i) \phi_i - 1} \exp \left( - \frac{(y_i - \beta_0 - \beta_1 m - \beta_2 - \beta_3 x_i)^2}{2 \delta^2} \right).
\]

Taken together, the complete log-likelihood function can be calculated as in equation (6).

### 7.2 Model for ZIB mediators and binary outcomes

The mediation model is very similar to the above case with binary outcomes. The only difference is that we use logistic regression for equation (7) since \( Y \) is a binary outcome.

The mediation model for binary outcomes can be formulated as follows:

\[
\log \left( \frac{P(Y = 1)}{1 - P(Y = 1)} \right) = \beta_0 + \beta_1 M + \beta_2 1(M > 0) + \beta_3 X,
\]

(12)

\[
\log \left( \frac{\mu_1 - \mu}{1 - \mu} \right) = \alpha_0 + \alpha_1 X,
\]

(13)

\[
\log (\phi) = \xi_0 + \xi_1 X,
\]

(14)

\[
\log \left( \frac{\Delta_1 - \Delta}{1 - \Delta} \right) = \gamma_0 + \gamma_1 X
\]

(15)

The formulas for NIE, NDE and CDE are:

\[
\text{NIE} = \text{NIE}_1 + \text{NIE}_2,
\]

\[
\text{NIE}_1 = \int_0^\infty \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_2}) dm
\]

\[
- \int_0^\infty \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_1}) dm,
\]

\[
\text{NIE}_2 = \Delta_{x_2} \expit(\beta_0 + \beta_3 x_2) - \Delta_{x_2} \int_0^\infty \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_2}) dm
\]

\[
- \Delta_{x_1} \expit(\beta_0 + \beta_3 x_2) + \Delta_{x_1} \int_0^\infty \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_1}) dm,
\]

\[
\text{NDE} = \Delta_{x_1} \expit(\beta_0 + \beta_3 x_2) + (1 - \Delta_{x_1}) \int_0^\infty \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_1}) dm
\]

\[
- \Delta_{x_1} \expit(\beta_0 + \beta_3 x_1) - (1 - \Delta_{x_1}) \int_0^\infty \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_1) G(m; \theta_{x_1}) dm,
\]

\[
\text{CDE} = \expit(\beta_0 + \beta_1 m + \beta_2 1(m > 0) + \beta_3 x_2) - \expit(\beta_0 + \beta_1 m + \beta_2 1(m > 0) + \beta_3 x_1),
\]

19
where
\[ G(m; \theta_x) = \frac{m^{\mu_x \phi_x - 1} (1 - m)^{(1 - \mu_x) \phi_x - 1}}{B(\mu_x \phi_x, (1 - \mu_x) \phi_x)}, \]
\[ \mu_x = \exp(\alpha_0 + \alpha_1 x), \]
\[ \phi_x = \exp(\xi_0 + \xi_1 x). \]

7.2.1 Log-likelihood function under the Probability mechanism with equation (3)

The log-likelihood contribution from the first group can be calculated as:
\[ l_1 = \log(f(y_i, r_i|m_i^*, x_i)f(m_i^*|x_i)) = \log(f(y_i|m_i^*, x_i)f(r_i|m_i^*, x_i)) \]
\[ = \log(f(y_i|m_i^*, x_i)) + \log(f(r_i|m_i^*)) + \log(f(m_i^*|x_i)) \]
\[ = \log \left( \frac{(\exp(\beta_0 + \beta_1 m_i^* + \beta_2 + \beta_3 x_i))^y_i}{1 + \exp(\beta_0 + \beta_1 m_i^* + \beta_2 + \beta_3 x_i)} \right) + \log(1 - \exp(-\eta^2 m_i^*)) \]
\[ + \log(1 - \Delta_i) - \log \left( B(\mu_i \phi_i, (1 - \mu_i) \phi_i) \right) \]
\[ + (\mu_i \phi_i - 1) \log(m_i^*) + ((1 - \mu_i) \phi_i - 1) \log(1 - m_i^*). \]

The log-likelihood contribution from the second group can be calculated as:
\[ l_2 = \log(f(y_i, r_i, m_i^*|x_i)) = \log \left( \int_0^1 f(y_i, r_i|m, x_i)dF(m|x_i) \right) \]
\[ = \log \left( \int_0^1 f(y_i|m, x_i)f(r_i|m)dF(m|x_i) \right) \]
\[ = \log \left( \frac{\Delta_i(\exp(\beta_0 + \beta_3 x_i))^y_i}{1 + \exp(\beta_0 + \beta_3 x_i)} \right) \]
\[ + \int_0^1 \left( \frac{\exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i))^y_i}{1 + \exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i)} \right) (1 - \Delta_i)G(m; \theta_x) \exp(-\eta^2 m)dm \]
\[ = \log \left( \frac{\Delta_i(\exp(\beta_0 + \beta_3 x_i))^y_i}{1 + \exp(\beta_0 + \beta_3 x_i)} + \frac{1 - \Delta_i}{B(\mu_i \phi_i, (1 - \mu_i) \phi_i)} \int_0^1 h_i(m)dm \right), \]

where
\[ h_i(m) = m^{\mu_i \phi_i - 1}(1 - m)^{(1 - \mu_i) \phi_i - 1} \left( \frac{\exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i))^y_i}{1 + \exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i)} \right) \exp(-\eta^2 m). \]

Taken together, the complete log-likelihood function can be calculated as in equation (6).

7.2.2 Log-likelihood function under the LOD mechanism with equation (4)

The log-likelihood contribution from the first group can be calculated as:
\[ l_1 = \log(f(y_i, r_i|m_i^*, x_i)f(m_i^*|x_i)) = \log(f(y_i|m_i^*, x_i)f(r_i|m_i^*, x_i)) \]
\[ f(m_i^*|x_i). \]
where $c$ by:

If the mediator $M$ has a ZILoN distribution, we have its two-part density function given by:

$$f(m; \theta) = \begin{cases} G(\theta), & m = 0 \\ (1 - G(\theta))G(m; \theta), & m > 0 \end{cases}$$

where $\theta = (\mu, \sigma, \Delta)$, $G(\theta) = \Delta$ and

$$G(m; \theta) = \frac{1}{m\sigma \sqrt{2\pi}} \exp \left( - \frac{(\log(m) - \mu)^2}{2\sigma^2} \right).$$

The transformation function and vectors in equation (2) are: $T(\theta) = (\mu, \log(\sigma), \log(\Delta/(1-\Delta))^T$, $\nu_0 = (\alpha_0, \xi_0, \gamma_0)^T$ and $\nu_1 = (\alpha_1, \xi_1, \gamma_1)^T$. We use identity link for $g(\cdot)$ in equation (1) since $Y$ is a continuous outcome. Then, the mediation model consists of the following equations:

$$Y = \beta_0 + \beta_1 M + \beta_2 1(M > 0) + \beta_3 X + \epsilon,$$
\[ \mu = \alpha_0 + \alpha_1 X, \]
\[ \log(\sigma) = \xi_0 + \xi_1 X, \]
\[ \log \left( \frac{\Delta}{1 - \Delta} \right) = \gamma_0 + \gamma_1 X, \]

where \( \epsilon \) follows a normal distribution with mean of zero and variance \( \delta^2 \). The average NIE, NDE and CDE for \( X \) changing from \( x_1 \) to \( x_2 \) are:

\[
\text{NIE} = E( Y_{x_2M_{x_2}} - Y_{x_2M_{x_1}} ) \\
= E(\beta_1(M_{x_2} - M_{x_1}) + \beta_2(1(\text{M}_{x_2}>0) - 1(\text{M}_{x_1}>0))) \\
= \beta_1(E(M_{x_2}) - E(M_{x_1})) + \beta_2(E(1(\text{M}_{x_2}>0)) - E(1(\text{M}_{x_1}>0))) \\
= \text{NIE}_1 + \text{NIE}_2, \\
\text{NIE}_1 = \beta_1 \left( \exp \left( \alpha_0 + \alpha_1 x_2 + \frac{\exp \left( 2(\xi_0 + \xi_1 x_2) \right)}{2} \right) \right. \\
\left. - \exp \left( \alpha_0 + \alpha_1 x_1 + \frac{\exp \left( 2(\xi_0 + \xi_1 x_1) \right)}{2} \right) \right) \\
\text{NIE}_2 = \beta_2(\expit(\gamma_0 + \gamma_1 x_1) - \expit(\gamma_0 + \gamma_1 x_2)) \\
\text{CDE} = E( Y_{x_2m} - Y_{x_1m} ) = \beta_3(x_2 - x_1). \\
\]

### 7.3.1 Log-likelihood function under the Probability mechanism with equation (3)

The log-likelihood contribution from the first group can be calculated as:

\[
l_1^1 = \log(f(y_i, r_i | m_i^*, x_i)) = \log(f(y_i | m_i^*, x_i)f(r_i | m_i^*, x_i)f(m_i^* | x_i)) \\
= \log(f(y_i | m_i^*, x_i)) + \log(f(r_i | m_i^*)) + \log(f(m_i^* | x_i)) \\
= -\log(\delta) - \frac{(y_i - \beta_0 - \beta_1 m_i^* - \beta_2 - \beta_3 x_i)^2}{2\delta^2} + \log(1 - \exp(-\eta^2 m_i^*)) \\
+ \log(1 - \Delta) - \log(m_i^* \sigma) - \frac{(\log(m_i^*) - \mu)^2}{2\sigma^2} + \text{cons.} \\
= -\log(\delta) - (\xi_0 + \xi_1 x_i) - \frac{(y_i - \beta_0 - \beta_1 m_i^* - \beta_2 - \beta_3 x_i)^2}{2\delta^2} + \log(1 - \exp(-\eta^2 m_i^*)) \\
+ \log \left( 1 - \expit(\gamma_0 + \gamma_1 x_i) \right) - \log(m_i^*) - \frac{(\log(m_i^*) - \alpha_0 - \alpha_1 x_i)^2}{2 \exp \left( 2(\xi_0 + \xi_1 x_i) \right)} + \text{cons}, \quad (17) \\
\]

The log-likelihood contribution from the second group can be calculated as:

\[
l_1^2 = \log(f(y_i, r_i | m_i^* | x_i)) = \log \left( \int_0^\infty f(y_i, r_i | m, x_i) dF(m|x_i) \right)
\]
The log-likelihood contribution from the second group can be calculated as:

\[ l^2_i = \log \left( \int_0^c f(y_i | m, x_i) f(r_i | m) dF(m | x_i) \right) \]

\[ = \log \left( \frac{\Delta_i}{\sqrt{2\pi \delta^2}} \exp \left( - \frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) \right) \]

\[ + \int_0^{\infty} f(y_i | m, x_i) \left( 1 - \frac{\Delta_i}{m \sigma \sqrt{2\pi}} \right) \exp \left( - \frac{(\log(m) - \mu)^2}{2\sigma^2} \right) \exp(-\eta^2 m) dm \]

\[ = - \log(\delta) + \log \left( \Delta_i \exp \left( - \frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) + \frac{(1 - \Delta_i) \exp(-\xi_0 - \xi_1 x_i)}{\sqrt{2\pi}} \int_0^{\infty} h_i(m) dm \right) \]

+ cons,

where

\[ h_i(m) = \exp \left( - \frac{(\log(m) - \alpha_0 - \alpha_1 x_i)^2}{2\exp(2(\xi_0 + \xi_1 x_i))} - \frac{(y_i - \beta_0 - \beta_1 m - \beta_2 - \beta_3 x_i)^2}{2\delta^2} - \eta^2 m \right) \frac{1}{m}. \]

Taken together, we have the complete log-likelihood function can be calculated by equation (6).

### 7.3.2 Log-likelihood function under LOD mechanism with equation (4)

The log-likelihood contribution from the first group can be calculated as:

\[ l^1_i = \log(f(y_i, r_i | m_i^*, x_i) f(m_i^* | x_i)) = \log(f(y_i | m_i^*, x_i) f(r_i | m_i^*, x_i) f(m_i^* | x_i)) \]

\[ = \log(f(y_i | m_i^*, x_i)) + \log(f(r_i | m_i^*)) + \log(f(m_i^* | x_i)) \]

\[ = - \log(\delta) - \frac{(y_i - \beta_0 - \beta_1 m_i^* - \beta_2 - \beta_3 x_i)^2}{2\delta^2} \]

\[ + \log(1 - \Delta_i) - \log(m_i^* \sigma) - \frac{(\log(m_i^*) - \mu)^2}{2\sigma^2} + \text{cons}. \]

\[ = - \log(\delta) - \left( \xi_0 + \xi_1 x_i \right) - \frac{(y_i - \beta_0 - \beta_1 m_i^* - \beta_2 - \beta_3 x_i)^2}{2\delta^2} \]

\[ + \log \left( 1 - \expit(\gamma_0 + \gamma_1 x_i) \right) - \log(m_i^*) - \frac{(\log(m_i^*) - \alpha_0 - \alpha_1 x_i)^2}{2\exp(2(\xi_0 + \xi_1 x_i))} + \text{cons}, \]

The log-likelihood contribution from the second group can be calculated as:

\[ l^2_i = \log(f(y_i, r_i, m_i^* | x_i)) = \log \left( \int_0^c f(y_i, r_i | m, x_i) dF(m | x_i) \right) \]

\[ = \log \left( \int_0^c f(y_i | m, x_i) f(r_i | m) dF(m | x_i) \right) \]

\[ = \log \left( \frac{\Delta_i}{\sqrt{2\pi \delta^2}} \exp \left( - \frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) \right) \]

\[ + \int_0^{\infty} f(y_i | m, x_i) \left( 1 - \frac{\Delta_i}{m \sigma \sqrt{2\pi}} \right) \exp \left( - \frac{(\log(m) - \mu)^2}{2\sigma^2} \right) \exp(-\eta^2 m) dm \]

\[ = - \log(\delta) + \log \left( \Delta_i \exp \left( - \frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) \right) \]

\[ + \int_0^{\infty} h_i(m) dm \]

\[ + \text{cons}, \]

where

\[ h_i(m) = \exp \left( - \frac{(\log(m) - \alpha_0 - \alpha_1 x_i)^2}{2\exp(2(\xi_0 + \xi_1 x_i))} - \frac{(y_i - \beta_0 - \beta_1 m - \beta_2 - \beta_3 x_i)^2}{2\delta^2} - \eta^2 m \right) \frac{1}{m}. \]
\[ + \int_{0}^{c} f(y_i|m, x_i) \left( \frac{1 - \Delta_i}{m\sigma\sqrt{2\pi}} \right) \exp \left( - \frac{(\log(m) - \mu)^2}{2\sigma^2} \right) \mathrm{d}m \]

\[ = - \log(\delta) + \log \left( \Delta_i \exp \left( - \frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) \right) + \frac{(1 - \Delta_i) \exp (-\xi_0 - \xi_1 x_i)}{\sqrt{2\pi}} \int_{0}^{c} h_i(m) \mathrm{d}m \]

+ \text{cons},

where

\[ h_i(m) = \exp \left( - \frac{(\log(m) - \alpha_0 - \alpha_1 x_i)^2}{2\exp(2(\xi_0 + \xi_1 x_i))} - \frac{(y_i - \beta_0 - \beta_1 m - \beta_2 - \beta_3 x_i)^2}{2\delta^2} \right) \]

Taken together, the complete log-likelihood function can be calculated as in equation (6).

### 7.4 Model for ZILoN mediators and binary outcomes

The mediation model is very similar to the above case and the only difference is that logistic regression is used here for the binary outcome \( Y \). Therefore, the mediation model consists of the following equations:

\[ \log \left( \frac{P(Y = 1)}{1 - P(Y = 1)} \right) = \beta_0 + \beta_1 M + \beta_2 1_{(M > 0)} + \beta_3 X, \]

\[ \mu = \alpha_0 + \alpha_1 X, \]

\[ \log(\sigma) = \xi_0 + \xi_1 X, \]

\[ \log \left( \frac{\Delta_i}{1 - \Delta} \right) = \gamma_0 + \gamma_1 X. \]

The average NIE, NDE and CDE for \( X \) changing from \( x_1 \) to \( x_2 \) are:

\[
\text{NIE} = \text{NIE}_1 + \text{NIE}_2,
\]

\[
\text{NIE}_1 = \int_{0}^{\infty} \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_2}) \mathrm{d}m
\]

\[
- \int_{0}^{\infty} \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_1}) \mathrm{d}m,
\]

\[
\text{NIE}_2 = \Delta_{x_2} \expit(\beta_0 + \beta_3 x_2) - \Delta_{x_2} \int_{0}^{\infty} \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_2}) \mathrm{d}m
\]

\[
- \Delta_{x_1} \expit(\beta_0 + \beta_3 x_2) + \Delta_{x_1} \int_{0}^{\infty} \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_1}) \mathrm{d}m,
\]

\[
\text{NDE} = \Delta_{x_1} \expit(\beta_0 + \beta_3 x_2) + (1 - \Delta_{x_1}) \int_{0}^{\infty} \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2) G(m; \theta_{x_1}) \mathrm{d}m
\]
The log-likelihood contribution from the second group can be calculated as:

\[- \Delta_i \expit(\beta_0 + \beta_3 x_i) - (1 - \Delta_i) \int_0^\infty \expit(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i) G(m; \theta_x) dm,\]

where

\[G(m; \theta_x) = \frac{1}{\exp (\xi_0 + \xi_1 x) m \sqrt{2\pi}} \exp \left( - \frac{(\log(m) - \alpha_0 - \alpha_1 x)^2}{2 \exp (2(\xi_0 + \xi_1 x))} \right).\]

### 7.4.1 Log-likelihood function under the Probability mechanism with equation (3)

The log-likelihood contribution from the first group can be calculated as:

\[l_i^1 = \log(f(y_i, r_i|m_i^*, x_i) f(m_i^*|x_i)) = \log(f(y_i|m_i^*, x_i) f(r_i|m_i^*, x_i) f(m_i^*|x_i))\]

\[= \log(f(y_i|m_i^*, x_i)) + \log(f(r_i|m_i^*)) + \log(f(m_i^*|x_i))\]

\[= \log \left( \frac{(\exp(\beta_0 + \beta_1 m_i^* + \beta_2 + \beta_3 x_i))^y_i}{1 + \exp(\beta_0 + \beta_1 m_i^* + \beta_2 + \beta_3 x_i)} \right) + \log(1 - \exp (-\eta^2 m_i))\]

\[+ \log(1 - \Delta_i) - \log(m_i^* \sigma) - \frac{(\log(m_i^*) - \mu)^2}{2\sigma^2} + \text{cons.}\]

\[= \log \left( \frac{(\exp(\beta_0 + \beta_1 m_i^* + \beta_2 + \beta_3 x_i))^y_i}{1 + \exp(\beta_0 + \beta_1 m_i^* + \beta_2 + \beta_3 x_i)} \right) + \log(1 - \exp (-\eta^2 m_i))\]

\[+ \log \left( 1 - \exp(\gamma_0 + \gamma_1 x_i) \right) - \log(m_i^*) - (\xi_0 + \xi_1 x_i) - \frac{(\log(m_i^*) - \alpha_0 - \alpha_1 x_i)^2}{2 \exp (2(\xi_0 + \xi_1 x_i))} + \text{cons.}\]

The log-likelihood contribution from the second group can be calculated as:

\[l_i^2 = \log(f(y_i, r_i, m_i^*|x_i)) = \log \left( \int_0^\infty f(y_i, r_i|m, x_i) dF(m|x_i) \right)\]

\[= \log \left( \int_0^\infty f(y_i|m, x_i) f(r_i|m) dF(m|x_i) \right)\]

\[= \log \left( \frac{\Delta_i (\exp(\beta_0 + \beta_3 x_i))^y_i}{1 - \exp(\beta_0 + \beta_3 x_i)} \right)\]

\[+ \int_0^\infty \frac{(\exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i))^y_i}{1 + \exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i)} \left( \frac{1 - \Delta_i}{m \sigma \sqrt{2\pi}} \right) \exp \left( - \frac{(\log(m) - \mu)^2}{2 \sigma^2} \right) \exp(-\eta^2 m) dm\]

\[= \log \left( \frac{\Delta_i (\exp(\beta_0 + \beta_3 x_i))^y_i}{1 + \exp(\beta_0 + \beta_3 x_i)} + \frac{(1 - \Delta_i) \exp(\xi_0 - \xi_1 x)}{\sqrt{2\pi}} \int_0^\infty h_i(m) dm \right),\]

where

\[h_i(m) = \frac{(\exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i))^y_i}{1 + \exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i)} \exp \left( - \frac{(\log(m) - \alpha_0 - \alpha_1 x)^2}{2 \exp (2(\xi_0 + \xi_1 x))} - \eta^2 m \right).\]

Taken together, we have the complete log-likelihood function can be calculated by equation (6).
7.4.2 Log-likelihood function under the LOD mechanism with equation (4)

The log-likelihood function from the first group can be calculated as:

\[ l_1^1 = \log(f(y_i, r_i|m_1^i, x_i)) = \log(f(y_i|m_1^i, x_i)f(r_i|m_1^i, x_i)f(m_1^i|x_i)) \]

\[ = \log(f(y_i|m_1^i, x_i)) + \log(f(r_i|m_1^i)) + \log(f(m_1^i|x_i)) \]

\[ = \log \left( \frac{\exp(\beta_0 + \beta_1 m_1^i + \beta_2 + \beta_3 x_i)^{y_i}}{1 + \exp(\beta_0 + \beta_1 m_1^i + \beta_2 + \beta_3 x_i)} \right) \]

\[ + \log(1 - \Delta_i) - \log(m_1^i\sigma) - \frac{(\log(m_1^i) - \mu)^2}{2\sigma^2} + \text{cons.} \]

The log-likelihood contribution from the second group can be calculated as:

\[ l_1^2 = \log(f(y_i, r_i, m_1^i|x_i)) = \log \left( \int_0^c f(y_i, r_i|m, x_i)dF(m|x_i) \right) \]

\[ = \log \left( \int_0^c f(y_i|m, x_i)f(r_i|m)dF(m|x_i) \right) \]

\[ = \log \left( \int_0^c \frac{\Delta_i(\exp(\beta_0 + \beta_3 x_i))^{y_i}}{1 - \exp(\beta_0 + \beta_3 x_i)} \right) \]

\[ + \int_0^c \frac{(\exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i)^{y_i}}{1 + \exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i)} \left( \frac{1 - \Delta_i}{m\sigma\sqrt{2\pi}} \right) \exp \left( -\frac{(\log(m) - \mu)^2}{2\sigma^2} \right) dm \]

\[ = \log \left( \frac{\Delta_i(\exp(\beta_0 + \beta_3 x_i))^{y_i}}{1 + \exp(\beta_0 + \beta_3 x_i)} + \frac{(1 - \Delta_i) \exp(-\xi_0 - \xi_1 x_i)}{\sqrt{2\pi}} \int_0^c h_i(m)dm \right), \]

where

\[ h_i(m) = \frac{\exp \left( \frac{-(\log(m) - \alpha_0 - \alpha_1 x_i)^2}{2\exp(2(\xi_0 + \xi_1 x_i))} \right)}{m}. \]

Taken together, the complete log-likelihood function can be calculated as in equation (6).

7.5 Model for ZIP mediators and continuous outcomes

If the mediator \( M \) has a ZIP distribution, its two-part density function can be written as:

\[ f(m; \theta) = \begin{cases} G(\theta), & m = 0 \\ (1 - G(\theta))G(m; \theta), & m > 0 \end{cases} \]

where \( \theta = (\lambda, \Delta^*) \), \( G(\theta) = \Delta^* + (1 - \Delta^*) \exp(-\lambda) \) and

\[ G(m; \theta) = \frac{\lambda^m}{m!(\exp(\lambda) - 1)}, m = 1, 2, \ldots \]
The log-likelihood contribution from the second group can be calculated as: $T(\theta) = (\log(\lambda), \log(\Delta^*/(1-\Delta^*)))^T$, $\nu_0 = (\alpha_0, \gamma_0)^T$ and $\nu_1 = (\alpha_1, \gamma_1)^T$. We use identity link for $g(\cdot)$ in equation (1) since $Y$ is a continuous outcome. The mediation model consists of the following equations:

\[
Y = \beta_0 + \beta_1 M + \beta_2 1_{(M>0)} + \beta_3 X + \epsilon,
\]

\[
\log(\lambda) = \alpha_0 + \alpha_1 X
\]

\[
\log \left( \frac{\Delta^*}{1-\Delta^*} \right) = \gamma_0 + \gamma_1 X.
\]

The formulas for NIE, NDE and CDE are

\[
\text{NIE} = E(Y_{x_2M_{x_2}} - Y_{x_2M_{x_1}})
\]

\[
= E(\beta_1(M_{x_2} - M_{x_1}) + \beta_2(1_{(M_{x_2}>0)} - 1_{(M_{x_1}>0)}))
\]

\[
= \beta_1E(M_{x_2}) - E(M_{x_1}) + \beta_2(E(1_{(M_{x_2}>0)}) - E(1_{(M_{x_1}>0)}))
\]

\[= \text{NIE}_1 + \text{NIE}_2,
\]

\[\text{NIE}_1 = \beta_1 \left( \exp(\alpha_0 + \alpha_1 x_2) - \exp(\alpha_0 + \alpha_1 x_1) \right)
\]

\[\text{NIE}_2 = \beta_2 \left( 1 - \expit(\gamma_0 + \gamma_1 x_2) \right) \left( 1 - e^{-\expit(\alpha_0 + \alpha_1 x_2)} \right)
\]

\[\quad - \left( 1 - \expit(\gamma_0 + \gamma_1 x_1) \right) \left( 1 - e^{-\expit(\alpha_0 + \alpha_1 x_1)} \right)
\]

\[\quad - \beta_1 \left( \expit(\gamma_0 + \gamma_1 x_2) \exp(\alpha_0 + \alpha_1 x_2) - \expit(\gamma_0 + \gamma_1 x_1) \exp(\alpha_0 + \alpha_1 x_1) \right)
\]

\[\text{NDE} = E(Y_{x_2M_{x_1}} - Y_{x_1M_{x_1}}) = \beta_3(x_2 - x_1),
\]

\[\text{CDE} = E(Y_{x_2m} - Y_{x_1m}) = \beta_3(x_2 - x_1)
\]

### 7.5.1 Log-likelihood function under the Probability mechanism with equation (3)

The log-likelihood contribution from the first group can be calculated as:

\[
l_i^1 = \log(f(y_i, r_i|m_i^*, x_i)f(m_i^*|x_i)) = \log(f(y_i|m_i^*, x_i)f(r_i|m_i^*, x_i)f(m_i^*|x_i))
\]

\[= \log(f(y_i|m_i^*, x_i)) + \log(f(r_i|m_i^*)) + \log(f(m_i^*|x_i))
\]

\[= -\log(\delta) - \frac{(y_i - \beta_0 - \beta_1 m_i^* - \beta_2 - \beta_3 x_i)^2}{2\delta^2} + \log(1 - \exp(-\eta^2 m_i^*))
\]

\[+ \log(1 - \Delta_i) + m_i^* \log(\lambda_i) - \log(\exp(\lambda_i) - 1) + \text{cons}.
\]

The log-likelihood contribution from the second group can be calculated as:

\[
l_i^2 = \log(f(y_i, r_i, m_i^*|x_i)) = \log \left( \sum_{m=0}^{\infty} f(y_i, r_i, m, x_i) dF(m|x_i) \right)
\]

\[= \log \left( \sum_{m=0}^{\infty} f(y_i|m, x_i)f(r_i|m)dF(m|x_i) \right)
\]

\[= \log \left( \frac{\Delta_i}{\sqrt{2\pi\delta^2}} \exp \left( -\frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) \right)
\]
The log-likelihood contribution from the second group can be calculated as:

\[
+ \sum_{m=1}^{\infty} f(y_i|m, x_i)(1 - \Delta_i) \frac{\lambda_i^m}{m!(\exp(\lambda_i) - 1)} \exp(-\eta^2 m)
\]

\[
= - \log(\delta) + \log \left( \Delta_i \exp \left( - \frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) + \frac{1 - \Delta_i}{\exp(\lambda_i) - 1} \sum_{m=1}^{\infty} h_i(m) \right)
\]

+ cons,

where \( \Delta_i = \Delta_i^* + (1 - \Delta_i^*) \exp(-\lambda_i) \) and

\[
h_i(m) = \exp \left( m \log(\lambda_i) - \frac{(y_i - \beta_0 - \beta_1 m^*_i - \beta_2 - \beta_3 x_i)^2}{2\delta^2} - \eta^2 m \right) / m!
\]

Taken together, the complete log-likelihood function can be calculated as in equation (6).

### 7.5.2 Log-likelihood function under the LOD mechanism with equation (4)

The log-likelihood contribution from the first group can be calculated as:

\[
l_i^1 = \log(f(y_i, r_i|m^*_i, x_i)f(m^*_i|x_i)) = \log(f(y_i|m^*_i, x_i)f(r_i|m^*_i, x_i)f(m^*_i|x_i))
\]

\[
= \log(f(y_i|m^*_i, x_i)) + \log(f(r_i|m^*_i)) + \log(f(m^*_i|x_i))
\]

\[
= - \log(\delta) - \frac{(y_i - \beta_0 - \beta_1 m^*_i - \beta_2 - \beta_3 x_i)^2}{2\delta^2}
\]

\[
+ \log(1 - \Delta_i) + m_i^* \log(\lambda_i) - \log(\exp(\lambda_i) - 1) + \text{cons}
\]

The log-likelihood contribution from the second group can be calculated as:

\[
l_i^2 = \log(f(y_i, r_i, m^*_i|x_i)) = \log \left( \sum_{m=0}^{[c]-1} f(y_i, r_i|m, x_i)dF(m|x_i) \right)
\]

\[
= \log \left( \sum_{m=0}^{\infty} f(y_i|m, x_i)f(r_i|m)dF(m|x_i) \right)
\]

\[
= \log \left( \frac{\Delta_i}{\sqrt{2\pi\delta^2}} \exp \left( - \frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) \right)
\]

\[
+ \sum_{m=1}^{[c]-1} f(y_i|m, x_i)(1 - \Delta_i) \frac{\lambda_i^m}{m!(\exp(\lambda_i) - 1)}
\]

\[
= - \log(\delta) + \log \left( \Delta_i \exp \left( - \frac{(y_i - \beta_0 - \beta_3 x_i)^2}{2\delta^2} \right) + \frac{1 - \Delta_i}{\exp(\lambda_i) - 1} \sum_{m=1}^{[c]-1} h_i(m) \right)
\]

+ cons,

where \([c]\) is the ceiling value of \(c\), \(\Delta_i = \Delta_i^* + (1 - \Delta_i^*) \exp(-\lambda_i) \) and

\[
h_i(m) = \frac{\exp \left( m \log(\lambda_i) - \frac{(y_i - \beta_0 - \beta_1 m^*_i - \beta_2 - \beta_3 x_i)^2}{2\delta^2} \right)}{m!}
\]

Taken together, the complete log-likelihood function can be calculated as in equation (6).
7.6 Model for ZIP mediators and binary outcomes

The mediation model is very similar to the above case and the only difference is that logistic regression is used here for the binary outcome $Y$. Therefore, the mediation model equations are given by:

\[
\log \left( \frac{P(Y = 1)}{1 - P(Y = 1)} \right) = \beta_0 + \beta_1 M + \beta_2 1(M > 0) + \beta_3 X,
\]

\[
\log (\lambda) = \alpha_0 + \alpha_1 X
\]

\[
\log \left( \frac{\Delta^*}{1 - \Delta^*} \right) = \gamma_0 + \gamma_1 X.
\]

The average NIE, NDE and CDE for $X$ changing from $x_1$ to $x_2$ are:

NIE = NIE$_1$ + NIE$_2$,

NIE$_1 = \sum_{m=1}^{\infty} \text{expit}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2)G(m; \theta_{x_2})$

\[ - \sum_{m=1}^{\infty} \text{expit}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2)G(m; \theta_{x_1}), \]

NIE$_2 = \Delta_{x_2} \text{expit}(\beta_0 + \beta_3 x_2) - \Delta_{x_2} \sum_{m=1}^{\infty} \text{expit}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2)G(m; \theta_{x_2})$

\[ - \Delta_{x_1} \text{expit}(\beta_0 + \beta_3 x_2) + \Delta_{x_1} \sum_{m=1}^{\infty} \text{expit}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2)G(m; \theta_{x_1}), \]

NDE = $\Delta_{x_1} \text{expit}(\beta_0 + \beta_3 x_2) + (1 - \Delta_{x_1}) \sum_{m=1}^{\infty} \text{expit}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2)G(m; \theta_{x_1})$

\[ - \Delta_{x_1} \text{expit}(\beta_0 + \beta_3 x_2) - (1 - \Delta_{x_1}) \sum_{m=1}^{\infty} \text{expit}(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_2)G(m; \theta_{x_1}), \]

CDE = $\text{expit}(\beta_0 + \beta_1 m + \beta_2 1_{(m > 0)} + \beta_3 x_2) - \text{expit}(\beta_0 + \beta_1 m + \beta_2 1_{(m > 0)} + \beta_3 x_1)$,

where

\[
G(m; \theta_x) = \frac{\lambda^m_x}{m!(\exp (\lambda_x) - 1)},
\]

\[
\Delta_x = \Delta^* + (1 - \Delta^*) \exp (-\lambda_x),
\]

\[
\lambda_x = \exp (\alpha_0 + \alpha_1 x),
\]

\[
\Delta^*_x = \expit(\gamma_0 + \gamma_1 x).
\]

7.6.1 Log-likelihood function under the Probability mechanism with equation (3)

The log-likelihood contribution from the first group can be calculated as:

\[
l_1^i = \log (f(y_i | r_i | m_i^*, x_i) f(m_i^* | x_i)) = \log (f(y_i | m_i^*, x_i) f(r_i | m_i^*, x_i) f(m_i^* | x_i))
\]
The log-likelihood contribution from the first group can be calculated as:

\[ l_1^2 = \log(f(y_i, r_i, m_i^* | x_i)) = \log \left( \sum_{m=0}^{\infty} f(y_i, r_i | m, x_i) dF(m | x_i) \right) \]

\[ = \log \left( \sum_{m=0}^{\infty} f(y_i | m, x_i) f(r_i | m) dF(m | x_i) \right) \]

\[ = \log \left( \frac{\Delta_i (\exp(\beta_0 + \beta_3 x_i))^{y_i}}{1 + \exp(\beta_0 + \beta_3 x_i)} \right) + \sum_{m=1}^{\infty} f(y_i | m, x_i)(1 - \Delta_i) \frac{\lambda_m^m}{m!(\exp(\lambda_i) - 1)} \exp(-\eta^2 m) \]

\[ = \log \left( \frac{\Delta_i (\exp(\beta_0 + \beta_3 x_i))^{y_i}}{1 + \exp(\beta_0 + \beta_3 x_i)} + \frac{1 - \Delta_i}{\exp(\lambda_i) - 1} \sum_{m=1}^{\infty} h_i(m) \right), \]

where \( \Delta_i = \Delta_i^* + (1 - \Delta_i^*) \exp(-\lambda_i) \) and

\[ h_i(m) = \frac{(\exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i))^{y_i}}{1 + \exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i)} \frac{\exp(m \log(\lambda_i) - \eta^2 m)}{m!}. \]

Taken together, the complete log-likelihood function can be calculated as in equation (6).

### 7.6.2 Log-likelihood function under the LOD mechanism with equation (4)

The log-likelihood contribution from the first group can be calculated as:

\[ l_1^1 = \log(f(y_i, r_i | m_i^* | x_i)) = \log(f(y_i | m_i^* | x_i) f(r_i | m_i^* | x_i) f(m_i^* | x_i)) \]

\[ = \log(f(y_i | m_i^* | x_i)) + \log(f(r_i | m_i^*)) + \log(f(m_i^* | x_i)) \]

\[ = \log \left( \frac{(\exp(\beta_0 + \beta_1 m_i^* + \beta_2 + \beta_3 x_i))^{y_i}}{1 + \exp(\beta_0 + \beta_1 m_i^* + \beta_2 + \beta_3 x_i)} \right) + \log(1 - \Delta_i) + m_i^* \log(\lambda_i) - \log(\exp(\lambda_i) - 1) + \text{cons.} \]

The log-likelihood contribution from the second group can be calculated as:

\[ l_i^2 = \log(f(y_i, r_i, m_i^* | x_i)) = \log \left( \sum_{m=0}^{c-1} f(y_i, r_i | m, x_i) dF(m | x_i) \right) \]

\[ = \log \left( \sum_{m=0}^{c-1} f(y_i | m, x_i) f(r_i | m) dF(m | x_i) \right) \]

\[ = \log \left( \frac{\Delta_i (\exp(\beta_0 + \beta_3 x_i))^{y_i}}{1 + \exp(\beta_0 + \beta_3 x_i)} \right) \]
\[
[\sum_{m=1}^{c \! - \! 1} f(y_i|m, x_i) (1 - \Delta_i) \frac{\lambda_i^m}{m!(\exp(\lambda_i) - 1)} ] 
= \log \left( \frac{\Delta_i (\exp(\beta_0 + \beta_3 x_i))^{y_i}}{1 + \exp(\beta_0 + \beta_2 x_i)} + \frac{1 - \Delta_i}{\exp(\lambda_i) - 1} \sum_{m=1}^{c \! - \! 1} h_i(m) \right),
\]
where \(\Delta_i = \Delta_i^* + (1 - \Delta_i^*) \exp(-\lambda_i)\) and
\[
h_i(m) = \frac{(\exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i))^{y_i}}{1 + \exp(\beta_0 + \beta_1 m + \beta_2 + \beta_3 x_i)} \frac{\exp(m \log(\lambda_i))}{m!}.
\]
Taken together, the complete log-likelihood function can be calculated as in equation (6).

### 7.7 All tables

| Parameter / Effect | True | Probability mechanism | LOD mechanism |
|------------------|-----|----------------------|---------------|
|                  | Mean| Bias | Bias % | SE | Mean SE | CP(%) | Mean| Bias | Bias % | SE | Mean SE | CP(%) |
| NIE1             | 0.025 | 0.028 | -0.001 | 12.0 | 0.002  | 0.01 | 92 | 0.026 | -0.001 | 4.0 | 0.002  | 0.02 | 93 |
| NIE2             | -0.670 | -0.774 | 0.104 | 15.5 | 0.028  | 0.27 | 94 | -0.778 | 0.108 | -16.1 | 0.028  | 0.26 | 94 |
| NIE              | -0.645 | -0.746 | 0.129 | -20.0 | 0.028  | 0.28 | 94 | -0.752 | 0.107 | -16.6 | 0.028  | 0.28 | 94 |
| NDE              | 0.100 | 0.989  | 0.011 | 1.1  | 0.006  | 0.06 | 91 | 0.995 | 0.005  | 0.5  | 0.006  | 0.06 | 94 |
| CDE              | 0.100 | 0.989  | 0.011 | 1.1  | 0.006  | 0.06 | 91 | 0.995 | 0.005  | 0.5  | 0.006  | 0.06 | 94 |
| \(\beta_0\)     | 1.000 | 1.058  | -0.058 | -5.8 | 0.022  | 0.17 | 100 | 0.995 | 0.005  | 0.5  | 0.006  | 0.06 | 94 |
| \(\beta_1\)     | 1.000 | 1.137  | -0.137 | -13.7 | 0.056  | 0.43 | 100 | 0.992 | 0.018  | 1.8  | 0.036  | 0.36 | 100 |
| \(\beta_2\)     | 1.000 | 0.989  | 0.011 | 1.1  | 0.006  | 0.06 | 91 | 0.995 | 0.005  | 0.5  | 0.006  | 0.06 | 94 |
| \(\beta_3\)     | 1.000 | 0.989  | 0.011 | 1.1  | 0.006  | 0.06 | 91 | 0.995 | 0.005  | 0.5  | 0.006  | 0.06 | 94 |
| \(\alpha_0\)    | 0.100 | 0.110  | -0.010 | -10.0 | 0.006  | 0.05 | 100 | 0.103 | -0.003 | -3.0 | 0.005  | 0.04 | 100 |
| \(\alpha_1\)    | 0.100 | 0.102  | -0.002 | -2.0  | 0.006  | 0.05 | 100 | 0.106 | -0.006 | -6.0 | 0.004  | 0.04 | 100 |
| \(\gamma_0\)    | 0.200 | 2.043  | -0.043 | -2.2  | 0.012  | 0.11 | 100 | 2.020 | -0.020 | -1.0 | 0.008  | 0.08 | 100 |
| \(\xi_0\)       | 0.100 | 0.095  | 0.005 | 5.0  | 0.013  | 0.12 | 100 | 0.106 | -0.006 | -6.0 | 0.01   | 0.009 | 100 |
| \(\gamma_1\)    | -2.000 | -2.054 | 0.054 | -2.7  | 0.019  | 0.19 | 100 | -2.054 | 0.054  | -2.7 | 0.019  | 0.19 | 100 |
| \(\sigma_0\)    | 0.500 | 0.580  | -0.080 | -16.0 | 0.019  | 0.19 | 100 | 0.580 | -0.080 | -16.0 | 0.019  | 0.19 | 100 |
| \(\delta\)      | 1.000 | 0.994  | 0.006 | 0.6  | 0.004  | 0.04 | 100 | 0.994 | 0.006  | 0.6  | 0.004  | 0.04 | 100 |
| \(\eta\)        | 1.500 | 1.495  | 0.005 | 0.3  | 0.006  | 0.07 | 100 | 1.500 | 1.495  | 0.005 | 0.3   | 0.006 | 0.07 | 100 |

| IKT approach     |     |        |       |     |        |     |     |        |       |     |        |
|------------------|-----|--------|-------|-----|--------|-----|-----|--------|-------|-----|--------|
| ACME(NIE)        | -0.645 | -0.001 | -0.644 | 99.8 | -    | -   | 0   | -0.009 | -0.636 | 98.6 | -    | 0     |
| ADE(NDE)         | 1.000 | 0.429  | 0.571 | 57.1 | -    | -   | 15  | 0.790  | 0.210  | 21.0 | -    | 61    |

Table 1: Simulation results for \(M\) with a ZIB distribution and a continuous \(Y\) with sample size of \(n = 300\). Bias, percentage of the bias, the empirical standard errors, the the mean of estimated standard errors and the empirical coverage probability of the 95% confidence interval for each estimator is respectively reported under the columns Bias, Bias %, SE, Mean SE and CP(%). Mediation effects from the IKT approach are provided at the bottom part of the table.
| Parameter / Effect | True | Probability mechanism | LOD mechanism | IKT approach |
|--------------------|------|-----------------------|---------------|--------------|
| NIE1               | 0.134| 0.186 -0.052 -38.8 0.017 0.17 94 | 0.197 -0.063 -47.0 0.018 0.18 95 | ACME(NIE) -0.040 -0.017 -0.023 57.5 - - 80 -0.025 -0.015 37.5 - - 86 |
| NIE2               | -0.200| -0.171 -0.029 14.5 0.023 0.24 96 | -0.177 -0.023 11.5 0.023 0.25 97 | ADE(NDE) 0.209 0.205 0.004 1.9 - - 98 0.219 -0.01 -4.8 - - 97 |
| NIE                | -0.066| 0.015 -0.081 122.7 0.027 27 96 | 0.020 -0.086 130.3 0.028 0.29 96 ||
| NDE                | 1.000| 0.960 0.040 4.0 0.007 0.07 94 | 0.970 0.030 3.0 0.006 0.07 94 ||
| CDE                | 1.000| 0.960 0.040 4.0 0.007 0.07 94 | 0.970 0.030 3.0 0.006 0.07 94 ||
| β_0                | 1.000| 2.267 -1.267 -126.7 0.067 27 100 | 1.944 -0.944 -94.4 0.069 0.23 100 ||
| β_1                | 1.000| 1.103 -0.103 -10.3 0.007 0.04 100 | 1.074 -0.074 -7.4 0.007 0.04 100 ||
| β_2                | 10.000| 8.295 1.705 17.1 0.083 34 100 | 8.756 1.244 12.4 0.089 0.28 100 ||
| β_3                | 1.000| 0.960 0.040 4.0 0.007 0.07 94 | 0.970 0.030 3.0 0.006 0.07 94 ||
| α_0                | -0.500| -0.417 -0.083 16.6 0.010 10 100 | -0.454 -0.046 9.2 0.006 0.08 100 ||
| α_1                | 0.100| 0.110 -0.010 10.0 0.009 0.09 100 | 0.105 -0.005 -5.0 0.008 0.08 100 ||
| ξ_0                | 0.200| 0.134 0.066 3.9 0.007 0.07 100 | 0.181 0.019 9.5 0.005 0.06 100 ||
| ξ_1                | 0.000| 0.033 -0.003 - 0.006 0.07 100 | 0.009 -0.009 - 0.005 0.06 100 ||
| γ_0                | -1.500| -1.492 -0.008 0.5 0.015 15 100 | -1.492 -0.008 0.5 0.015 0.15 100 ||
| γ_1                | 1.000| 0.082 0.018 18.0 0.014 15 100 | 0.082 0.018 18.0 0.014 0.15 100 ||
| δ                  | 1.000| 1.195 -0.195 -19.5 0.015 0.09 100 | 1.126 -0.126 -12.6 0.013 0.07 99 ||
| η                  | 1.300| 1.254 0.046 3.5 0.009 0.08 100 | 1.019 0.251 20.1 - - 95 ||

Table 2: Simulation results for \( M \) with a ZIB distribution and a binary \( Y \) with sample size \( n = 300 \). Bias, percentage of the bias, the empirical standard errors, the mean of estimated standard errors and the empirical coverage probability of the 95% confidence interval for each estimator is respectively reported under the columns Bias, Bias %, Mean SE, Mean SE and CP(%). Mediation effects from the IKT approach are provided at the bottom part of the table.

| Parameter / Effect | True | Probability mechanism | LOD mechanism | IKT approach |
|--------------------|------|-----------------------|---------------|--------------|
| RDNIE1             | -0.019| -0.019 0.000 0.0 0.002 0.02 91 | -0.022 0.003 -15.8 0.003 0.02 89 ||
| RDNIE2             | -0.021| -0.023 0.002 -9.5 0.002 0.02 93 | -0.020 -0.001 4.8 0.002 0.03 90 ||
| RDNIE              | -0.040| -0.042 0.002 -5.0 0.002 0.02 94 | -0.042 0.002 -5.0 0.002 0.02 98 ||
| RDNDE              | 0.209| 0.212 -0.003 -1.4 0.003 0.03 94 | 0.212 -0.003 -1.4 0.003 0.03 97 ||
| RDDE               | 0.199| 0.201 -0.002 -1.0 0.003 0.03 94 | 0.204 -0.005 -2.5 0.003 0.03 96 ||
| β_0                | -1.000| -1.091 0.091 -9.1 0.117 0.97 100 | -1.283 0.283 -28.3 0.129 1.38 100 ||
| β_1                | 1.000| 1.114 -0.114 -11.4 0.137 11.8 100 | 1.280 -0.280 -28.0 0.163 1.76 100 ||
| β_2                | 1.000| 1.054 -0.054 -5.4 0.020 0.20 100 | 1.069 -0.069 -6.9 0.019 0.19 100 ||
| α_0                | -0.500| -0.511 -0.01 9.8 0.007 0.08 100 | -0.474 -0.026 5.2 0.007 0.08 100 ||
| α_1                | -0.500| -0.474 -0.026 5.2 0.005 0.05 100 | -0.486 -0.014 2.8 0.005 0.05 100 ||
| ξ_0                | 2.000| 2.043 -0.043 -2.2 0.012 0.12 100 | 2.043 -0.043 -2.2 0.012 0.13 100 ||
| ξ_1                | -1.000| -0.984 -0.016 1.6 0.011 0.11 100 | -0.980 -0.020 2.0 0.011 0.12 100 ||
| γ_0                | 0.500| 0.677 -0.177 -14.4 0.046 0.38 100 | 0.534 -0.044 -6.8 0.031 0.32 100 ||
| γ_1                | 2.000| 2.353 -0.353 -17.7 0.059 0.64 100 | 2.000 2.353 -0.353 -17.7 0.059 0.64 100 ||

Table 3: Simulation results for \( M \) with a ZILoN distribution and a continuous \( Y \) with sample size \( n = 300 \). Bias, percentage of the bias, the empirical standard errors, the mean of estimated standard errors and the empirical coverage probability of the 95% confidence interval for each estimator is respectively reported under the columns Bias, Bias %, Mean SE, Mean SE and CP(%). Mediation effects from the IKT approach are provided at the bottom part of the table.
### Table 4: Simulation results for M with a ZILoN distribution and a binary Y with sample size n = 300.

| Parameter / Effect | Probability mechanism | LOD mechanism |
|--------------------|-----------------------|---------------|
|                    | Mean Estimate | Bias % | SE | Mean SE | Mean CP(%) | Mean Estimate | Bias % | SE | Mean SE | Mean CP(%) |
| Our approach       |              |       |   |        |           |              |       |   |        |           |
| RDNIE1             | 0.026        | 0.028 | -0.002 | -7.7 | 0.001 | 0.01 | 92 | 0.027 | -0.001 | -3.8 | 0.001 | 0.01 | 89 |
| RDNIE2             | -0.035       | -0.039 | 0.004 | -11.4 | 0.003 | 0.03 | 89 | -0.034 | -0.001 | -2.9 | 0.003 | 0.02 | 89 |
| RDNIE              | -0.010       | -0.010 | 0.000 | 0.0 | 0.003 | 0.03 | 87 | -0.007 | -0.003 | 30.0 | 0.003 | 0.02 | 89 |
| RDNDE              | 0.181        | 0.173 | 0.008 | 4.4 | 0.003 | 0.03 | 92 | 0.172 | 0.009 | 5.0 | 0.002 | 0.03 | 93 |
| RDCDE              | 0.028        | 0.029 | -0.001 | -3.6 | 0.002 | 0.02 | 86 | 0.028 | 0.000 | 0.0 | 0.002 | 0.02 | 85 |
| β_0                | -1.000       | -1.121 | 0.121 | -12.1 | 0.083 | 0.85 | 100 | -1.059 | 0.059 | -5.9 | 0.077 | 0.70 | 100 |
| β_1                | 1.000        | 1.068 | -0.068 | -6.8 | 0.031 | 0.32 | 100 | 1.084 | -0.084 | -8.4 | 0.031 | 0.31 | 100 |
| β_2                | 1.000        | 1.133 | -0.133 | -13.3 | 0.100 | 0.98 | 100 | 1.044 | -0.044 | -4.4 | 0.091 | 0.85 | 100 |
| β_3                | 1.000        | 1.013 | -0.013 | -1.3 | 0.022 | 0.21 | 100 | 0.990 | 0.010 | 30.0 | 0.020 | 0.22 | 100 |
| α_0                | -0.010       | 0.032 | -0.042 | 420.0 | - | - | 31 | 0.032 | -0.042 | 420.0 | - | - | 30 |
| α_1                | 0.181        | 0.086 | 0.095 | 52.5 | - | - | 18 | 0.086 | 0.095 | 52.5 | - | - | 13 |
| ξ_0                | 0.500        | 0.460 | 0.040 | 8.0 | 0.009 | 0.08 | 100 | 0.456 | 0.044 | 8.8 | 0.009 | 0.09 | 100 |
| ξ_1                | 0.500        | 0.510 | -0.010 | -2.0 | 0.019 | 0.18 | 100 | 0.463 | 0.037 | 7.4 | 0.021 | 0.17 | 100 |
| γ_0                | 1.500        | 1.800 | -0.800 | -80.0 | 0.068 | 0.23 | 99 | 1.203 | -0.203 | -20.3 | 0.042 | 0.17 | 100 |
| γ_1                | 0.010        | 0.167 | -0.157 | -157.0 | 0.011 | 0.04 | 99 | 0.036 | -0.026 | -260.0 | 0.005 | 0.03 | 100 |
| γ_2                | 15.000       | 13.400 | 1.600 | 10.7 | 0.123 | 0.37 | 99 | 14.650 | 0.350 | 2.3 | 0.063 | 0.22 | 100 |
| γ_3                | 1.000        | 0.941 | 0.059 | 5.9 | 0.028 | 0.29 | 92 | 0.988 | 0.012 | 1.2 | 0.006 | 0.06 | 95 |
| δ_0                | -1.500       | -1.378 | -0.122 | -8.1 | 0.048 | 0.81 | 100 | -1.429 | -0.071 | -4.7 | 0.045 | 0.52 | 100 |
| η                  | 2.000        | 2.122 | -0.122 | -6.1 | 0.031 | 0.46 | 100 | 0.426 | 0.074 | 14.8 | 0.042 | 0.36 | 100 |
| IKT approach       |              |       |   |        |           |              |       |   |        |           |
| ACME(RDNIE)        | -0.010       | 0.032 | -0.042 | 420.0 | - | - | 31 | 0.032 | -0.042 | 420.0 | - | - | 30 |
| ADE(RDNDE)         | 0.181        | 0.066 | 0.095 | 52.5 | - | - | 18 | 0.086 | 0.095 | 52.5 | - | - | 13 |

### Table 5: Simulation results for M with a ZIP distribution and a continuous Y with sample size n = 300.

| Parameter / Effect | Probability mechanism | LOD mechanism |
|--------------------|-----------------------|---------------|
|                    | Mean Estimate | Bias % | SE | Mean SE | Mean CP(%) | Mean Estimate | Bias % | SE | Mean SE | Mean CP(%) |
| Our approach       |              |       |   |        |           |              |       |   |        |           |
| NE1                | 0.005        | 0.072 | -0.013 | -13.4 | 0.006 | 0.04 | 60 | 0.018 | -0.009 | -260.0 | 0.003 | 0.01 | 87 |
| NE2                | 0.100        | 0.167 | -0.157 | -157.0 | 0.011 | 0.04 | 99 | 0.036 | -0.026 | -260.0 | 0.005 | 0.03 | 100 |
| NDE                | 1.000        | 1.800 | -0.800 | -80.0 | 0.068 | 0.23 | 99 | 1.203 | -0.203 | -20.3 | 0.042 | 0.17 | 100 |
| CDE                | 1.000        | 1.941 | 0.059 | 5.9 | 0.008 | 0.07 | 88 | 0.988 | 0.012 | 1.2 | 0.006 | 0.06 | 95 |
| β_0                | 1.000        | 1.087 | -0.087 | -8.7 | 0.021 | 0.2 | 100 | -2.077 | 0.077 | -3.9 | 0.022 | 0.2 | 100 |
| β_1                | 1.000        | 1.517 | -0.017 | -1.1 | 0.004 | 0.04 | 100 | 1.462 | 0.038 | 2.5 | 0.004 | 0.03 | 100 |
| β_2                | 1.000        | 0.482 | 0.018 | 3.6 | 0.002 | 0.06 | 100 | 1.011 | -0.011 | -1.1 | 0.005 | 0.04 | 100 |

| IKT approach       |              |       |   |        |           |              |       |   |        |           |
| ACME(NDE)          | 0.059        | 0.030 | 0.029 | 83.1 | - | - | 49 | 0.020 | 0.039 | 66.1 | - | - | 61 |
| ADE(NDE)           | 1.000        | 0.826 | 0.174 | 17.4 | - | - | 89 | 0.668 | 0.332 | 33.2 | - | - | 71 |
Table 6: Simulation results for $M$ with a ZIP distribution and a binary $Y$ with sample size $n = 300$. Bias, percentage of the bias, the empirical standard errors, the mean of estimated standard errors and the empirical coverage probability of the 95% confidence interval for each estimator is respectively reported under the columns Bias, Bias %, SE, Mean SE and CP(%). Mediation effects from the IKT approach are provided at the bottom part of the table.

| Parameter | True Effect | Bias | Bias % | SE | Mean SE | CP(%) | Bias | Bias % | SE | Mean SE | CP(%) |
|-----------|-------------|------|--------|----|---------|-------|------|--------|----|---------|-------|
| Our approach | | | | | | | | | | | |
| RDNIE1 | 0.000 | 0.000 | 0.0 | 5×10^{-6} | 5×10^{-5} | 82 | 0.000 | 0.000 | - | 4×10^{-6} | 4×10^{-5} | 78 |
| RDNIE2 | 0.359 | 0.389 | -0.030 | 8.4 | 0.006 | 0.07 | 93 | 0.322 | 0.037 | 10.3 | 0.004 | 0.04 | 82 |
| RDNIE | 0.359 | 0.389 | -0.030 | 8.4 | 0.006 | 0.07 | 93 | 0.322 | 0.037 | 10.3 | 0.004 | 0.04 | 82 |
| RDNDE | 0.081 | 0.069 | 0.012 | 14.8 | 0.003 | 0.03 | 89 | 0.103 | -0.022 | -27.2 | 0.003 | 0.03 | 92 |
| IKT approach | | | | | | | | | | | |
| ACME(RDNIE) | 0.359 | -0.292 | 0.651 | 181.3 | - | - | 0 | -0.098 | 0.457 | 127.3 | - | - | 0 |
| ADE(RDNDE) | 0.081 | 0.053 | 0.028 | 34.6 | - | - | 53 | 0.087 | -0.006 | -7.4 | - | - | 96 |

Table 7: Results for the NHBCS

| OTU | Zero-inflated beta | Our approach | IKT approach |
|-----|-------------------|---------------|---------------|
| g.Sphingomonadales | 0.00 (-0.01, 0.01) | 0.224 | -0.03 (-0.06, -0.01) |
| g.Coprobacillus | 0.00 (-0.02, 0.02) | 0.983 | -0.08 (-0.15, -0.01) |

Table 8: Results for the VSL#3 mouse study
Figure 1: Mediation analysis for a zero-inflated mediator. Here $\nu$ denote the impact of the exposure $X$ on the mediator $M$ including the impacts on both parts of the two-part distribution.
Figure 2: Results for the NHBCS study. Two genera (*Sphingomonadales* and *Coprobacillus*) were found to mediate the effect of *in utero* arsenic on cough that resulted in a prescribed medicine. *Sphingomonadales* and *Coprobacillus* are highlighted in blue bars in the phylogenetic tree constructed using the NHBCS data. Taxa with mean relative abundance of > 5% are annotated in the figure.
Figure 3: Results for the VSL#3 mouse model. Four OTU’s were found to mediate the effect of VSL#3 on the dysplasia score. They are highlighted in blue bars in the phylogenetic tree constructed using the VSL#3 study data. One of four OTU’s is not highlighted because it did not have taxonomic assignment beyond the Kingdom level. Taxa with mean relative abundance of > 5% are annotated in the figure.