Mediation analysis with the mediator and outcome missing not at random

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Motivation

Mediation analysis: a useful and widely adopted approach for investigating the direct and indirect causal pathways through which an effect arises.

However, many mediation studies are challenged by missingness in the mediator and/or the outcome.
Job Corps: the largest education and training program for 16-24 year old disadvantaged youths administered by the U.S. Department of Labor.

A research question:

- Educational or vocational attainment
- Job Corps
- Earnings
A motivating study: National Job Corps Study (NJCS)

Table 1: Missingness patterns in the mediator and the outcome

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Outcome</th>
<th>Treatment $N$ (%)</th>
<th>Control $N$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>Observed</td>
<td>545 (10.72%)</td>
<td>361 (9.96%)</td>
</tr>
<tr>
<td>Observed</td>
<td>Missing</td>
<td>538 (10.58%)</td>
<td>400 (11.04%)</td>
</tr>
<tr>
<td>Missing</td>
<td>Missing</td>
<td>497 (9.78%)</td>
<td>426 (11.76%)</td>
</tr>
<tr>
<td>Observed</td>
<td>Observed</td>
<td>3504 (68.92%)</td>
<td>2436 (67.24%)</td>
</tr>
</tbody>
</table>

- Concern: the missingness may be missing not at random (MNAR).
- Example: the missingness in the mediator may depend on whether or not the subject received certificate.
Challenge: the underlying data distribution can not be identified in general without further assumptions if MNAR.

Most of the previous literature assume either missingness completely at random or missingness at random. (Enders et al., 2013; Zhang and Wang, 2013; Wu and Jia, 2013; Qin et al., 2021)

Consider missingness in outcomes only, Li and Zhou (2017) utilized an instrumental variable type of covariate to identify the direct and indirect effect when the missingness in the outcome is MNAR.
Outline

1. Notation and Basic Assumptions
2. Identification under MNAR: missingness only in the mediator
3. Identification under MNAR: missingness both in the mediator and outcome
4. Application to the Job Corps Study
5. Summary
Notation

- $T$: treatment assignment, $t = 1$ if assigned to the experimental group; $t = 0$ otherwise.
- $M(t)$: potential mediator value under treatment condition $t$.
- $Y(t, M(t))$, or equivalently, $Y(t)$: potential outcome value under treatment condition $t$.
- $X$: vector of measured covariates values.
- $M$ and $Y$: observed value of the mediator and the outcome.
Mediation analysis without missing data

ATE = NIE + NDE

\[ ATE = E[Y(1) - Y(0)] \equiv E[Y(1, M(1)) - Y(0, M(0))] \]

\[ \text{NIE} = E[Y(1, M(1)) - Y(1, M(0))] \]

\[ \text{NDE} = E[Y(1, M(0)) - Y(0, M(0))] \]

Sequential Ignorability Assumption (Imai et al., 2010a,b):

For \( t, t' \in \{0, 1\}, \)

\[ \{Y(t', m), M(t)\} \perp \perp T \mid X = x \]

\[ Y(t', m) \perp \perp M(t) \mid T = t, X = x \]
Mediation analysis without missing data

- Nonparametric identification result under sequential ignorability assumption when there exists no missing data:

\[ \mathbb{E}[Y(t, M(t')) | X = x] = \int \mathbb{E}[Y | T = t, M = m, X = x] \, dF(m | T = t', X = x) \]

- When there exists missing data, the key would be to identify:
  1. \( P(Y = y | T = t, M = m, X = x) \)
  2. \( P(M = m | T = t, X = x) \)

Or equivalently, \( P(Y = y, M = m | T = t, X = x) \)
Outline

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Missingness mechanisms: MCAR and MAR

$R^M$: missingness indicator of $M$, 1 if observed and 0 otherwise.

All graphs condition on $X$.

- If $R^M \perp M, Y, T, X$, the missingness is MCAR.
- If $R^M \perp M \mid Y, T, X$, the missingness is MAR.

However, in the Job Corps study, we are concerned that people who failed to obtain an educational or vocational certificate were less likely to report compared to people who successfully obtained an educational or vocational certificate.
Proposed MNAR mechanism

- MNAR Assumption I: $R^M \perp \!\!\!\!\perp Y \mid (M, T, X)$. 
- Allows the missingness $R^M$ to depend on the missing value $M$. 
- Since the outcome $Y$ occurs later, it is plausible in many studies to assume that the missingness of the mediator is conditionally independent of the outcome.
Identifiability under MNAR Assumption I

1. \[ P(Y = y \mid M = m, T = t, X = x) = P(Y = y \mid M = m, T = t, R^M = 1, X = x). \]

2. Define

\[ P_{my1|t,x} = P(M = m, Y = y, R^M = 1 \mid T = t, X = x), \]

\[ P_{+y0|t,x} = P(Y = y, R^M = 0 \mid T = t, X = x). \]

Then

\[ P_{+y0|t,x} = \sum_{m \in \mathcal{M}} P(M = m, Y = y, R^M = 0 \mid T = t, X = x) \]

\[ = \sum_{m \in \mathcal{M}} P_{my1|t,x} \frac{P(R^M = 0 \mid M = m, T = t, X = x)}{P(R^M = 1 \mid M = m, T = t, X = x)}. \]

Note that if the ratios are identifiable, then, \( P(M = m \mid T = t, X = x) \) can be identified by

\[ P(M = m \mid T = t, X = x) = \frac{P(M = m, R^M = 1 \mid T = t, X = x)}{P(R^M = 1 \mid M = m, T = t, X = x)}. \]
When will the ratios be identifiable?

$$P_{+y0|t,x} = \sum_{m \in \mathcal{M}} P_{my1|t,x} \frac{P(R^M = 0 | M = m, T = t, X = x)}{P(R^M = 1 | M = m, T = t, X = x)}.$$

- The ratios are identifiable if the above system of linear equations has full rank, which essentially requires that:
  1. The number of elements in the support of $Y$ is not smaller than the number of elements in the support of $M$.
  2. $M \not\perp\!
\!\!\perp Y | T, X$. 

Completeness condition

Completeness: Define a function \( f(A, B) \) to be complete in \( B \) if
\[
\int g(A) f(A, B) \, d\nu(A) = 0
\]
implies \( g(A) = 0 \) almost surely for any square-integrable function \( g \). Here, \( \nu(\cdot) \) denotes a generic measure.

The assumption of completeness is routinely made in nonparametric identification problems.

The completeness condition holds under some frequently used parametric models, such as exponential families of distributions (Newey and Powell, 2003) and a class of location-scale distribution families (Hu and Shiu, 2018).
Identifiability under MNAR Assumption I

**Theorem 1**

Under sequential ignorability and MNAR Assumption I, if

\[ P(R^M = 1 \mid M = m, T = t, X = x) > 0 \text{ for all } m, t, x, \text{ and if} \]

\[ P(Y, M, R^M = 1 \mid T = t, X = x) \text{ is complete in } Y \text{ for all } t, x, \]

\[ P(Y, M \mid T, X) \text{ is identifiable, and therefore, the NIE and NDE are identifiable.} \]

Since \( P(Y \mid M, T, X) \) can be identified without completeness, when \( M \perp \perp Y \mid T, X \), we have \( P(Y \mid M, T, X) = P(Y \mid T, X) \), NIE = 0 and

\[ \text{NDE} = \text{ATE} = \int_X [\mathbb{E}(Y \mid T = 1, X = x) - \mathbb{E}(Y \mid T = 0, X = x)]dF(x). \]
Simulation study under MNAR Assumption I

Four setups with different relationships in the supports of \( M \) and \( Y \):

(A) binary \( M \) and binary \( Y \), (B) binary \( M \) and continuous \( Y \),
(C) continuous \( M \) and continuous \( Y \), (D) continuous \( M \) and binary \( Y \).

\[ X \sim N(0,1), \ T \sim \text{Bernoulli}(0.5) \]

\[ M : \text{logit} \ P(M = 1 \mid T, X) = \alpha_0 + \alpha_t T + \alpha_x X, \ M \sim N(\alpha_0 + \alpha_t T + \alpha_x X, 1) \]

\[ Y : \text{logit} \ P(Y = 1 \mid M, T, X) = \beta_0 + \beta_m M + \beta_t T + \beta_{mt} M \cdot T + \beta_x X, \]
\[ Y \sim N(\beta_0 + \beta_m M + \beta_t T + \beta_{mt} M \cdot T + \beta_x X, 1) \]

\[ R^M : \text{logit} \ P(R^M = 1 \mid M, T, X) = \lambda_0 + \lambda_m M + \lambda_t T + \lambda_x X \]

Missing rates in \( M \): 20 ~ 25\% (with \( \lambda_m \neq 0 \))

500 simulated data sets with sample size 1000

Methods we compare:

1. Complete Case: using subjects without missing data
2. Multiple Imputation: by chained equations assuming MAR
3. Our EM Algorithm: incorporating the MNAR mechanism
4. Oracle: with true values of the missing data
Simulation results under MNAR Assumption I

- $M \not\perp Y \mid T, X$

- $M \perp Y \mid T, X$
The distribution of parameters may display multimodality and other irregular patterns when the nonparametric identification cannot be achieved.

\(M\) has more categories than \(Y\) where \(M\) is generated by a multinomial logistic regression model and \(Y\) is generated by a logistic regression model.

Simulation results on parameters in the \(M\) and \(R^M\) models.
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5. Summary
$R^Y$: the missingness indicator of $Y$, 1 if observed and 0 otherwise.

If $(R^M, R^Y) \perp (M, Y, T, X)$, the missingness is MCAR.

If $(R^M, R^Y) \perp (M, Y) | T, X$, the missingness is MAR.
MNAR Assumption II:

- $(R^Y, R^M) \perp Y \mid M, T, X$ and $R^Y \perp M \mid R^M, T, X$.
- MAR is a special case of the proposed MNAR Assumption II.
Theorem 2

Under sequential ignorability and MNAR Assumption II, if
\[ P(R^M = 1, R^Y = 1 \mid M = m, T = t, X = x) > 0 \] and
\[ P(R^M = 0, R^Y = 1 \mid M = m, T = t, X = x) > 0 \] for all \( m, t, x \), and if the
\[ P(Y, M, R^M = 1, R^Y = 1 \mid T = t, X = x) \] is complete in \( Y \) for all \( t, x \), the
\( P(Y, M \mid T, X) \) is identifiable, and therefore, the NIE and NDE are identifiable.

The completeness is only used to identify \( P(M \mid T, X) \), and therefore, when \( M \perp \perp Y \mid T, X \), we have \( P(Y \mid M, T, X) = P(Y \mid T, X) \), NIE = 0 and NDE = ATE.
MNAR Assumption III:

- $R^M \perp (R^M, M) \mid Y, T, X$ and $R^M \perp (R^Y, Y) \mid M, T, X$.
- It allows both the missingness of $M$ and the missingness of $Y$ to depend on the missing value itself.
Identification Result under MNAR Assumption III

Theorem 3

Under sequential ignorability and MNAR Assumption III, if

\[ P(R^M = 1, R^Y = 1 \mid Y = y, M = m, T = t, X = x) > 0, \]
\[ P(R^M = 0, R^Y = 1 \mid Y = y, M = m, T = t, X = x) > 0 \] and
\[ P(R^M = 1, R^Y = 0 \mid Y = y, M = m, T = t, X = x) > 0 \] for all \( y, m, t, x \), and if
\[ P(Y, M, R^M = 1, R^Y = 1 \mid T = t, X = x) \] is complete in \( Y \) for all \( t, x \), and if
\[ P(Y, M, R^M = 1, R^Y = 1 \mid T = t, X = x) \] is also complete in \( M \) for all \( t, x \),
\[ P(Y, M \mid T, X) \] is identifiable, and therefore, the NIE and NDE are identifiable.

Different from before, the identification of both \( P(Y \mid M, T, X) \) and \( P(M \mid T, X) \) rely on the above completeness conditions, and therefore, when \( M \perp \perp Y \mid T, X \), the NIE and NDE are no longer identifiable.
Simulation study under MNAR Assumption III

- $R^M$: logit $P(R^M = 1 \mid M, T, X) = \lambda_0 + \lambda_m M + \lambda_t T + \lambda_x X$
- $R^Y$: logit $P(R^Y = 1 \mid Y, T, X) = \gamma_0 + \gamma_y Y + \gamma_t T + \gamma_x X$
- Missing rates in $M$ and $Y$: 20 ~ 25\% \text{ (with } \lambda_m \neq 0, \gamma_y \neq 0)$
Simulation results under MNAR Assumption III

- $M \not\perp Y \mid T, X$

- $M \perp Y \mid T, X$

[Box plots showing bias values for different conditions under Assumptions A.III, B.III, C.III, and D.III.]
MNAR Assumption IV:

- $R^Y$, $R^M$ and $Y$ are mutually independent given $M, T, X$.
- The mediator $M$ drives the missingness in both $M$ and $Y$ given $T, X$. 
Identification Result under MNAR Assumption IV

Theorem 4

Under sequential ignorability and MNAR Assumptions IV, if either of the following two conditions holds, the joint distribution $P(Y, M \mid T, X)$ is identifiable, and therefore, the NIE and NDE are identifiable:

(i) $P(R^M = 1, R^Y = 1 \mid M = m, T = t, X = x) > 0$, $P(R^M = 0, R^Y = 1 \mid M = m, T = t, X = x) > 0$ and $P(R^M = 1, R^Y = 0 \mid M = m, T = t, X = x) > 0$ for all $m, t, x$, and $P(Y, M, R^M = 1, R^Y = 1 \mid T = t, X = x)$ is complete in $Y$ for all $t, x$;

(ii) $P(R^M = 1 \mid M = m, T = t, X = x) > 0$ for all $m, t, x$ and $P(M, R^M = 1, R^Y \mid T = t, X = x)$ is complete in $R^Y$ for all $t, x$.

- The completeness is only used to identify $P(M \mid T, X)$, and therefore, when $M \perp \perp Y \mid T, X$, we have $P(Y \mid M, T, X) = P(Y \mid T, X)$, NIE = 0 and NDE = ATE.
Assuming $Y$ is not affecting $R^M$, and allowing $M$ to have an impact on $R^M$, we have shown that identification of NIE and NDE can be achieved under some completeness assumptions when $R^Y$ only depend on one of $(R^M, Y, M)$ given $T, X$.

MNAR Assumption II

MNAR Assumption III

MNAR Assumption IV
When $R^Y$ depend on more than one of $(R^M, Y, M)$ given $T, X$, the identification of NIE and NDE cannot be achieved without further assumptions.

(i) unidentifiable case

(ii) unidentifiable case

(iii) unidentifiable case

(iv) unidentifiable case
We provide some scenarios where the identification is plausible under the unidentifiable cases by exploiting the information on a future outcome ($Y^*$).

\begin{align*}
\begin{array}{c}
R^M \rightarrow R^Y \\
\downarrow \\
M \rightarrow Y \\
\downarrow \\
Y^*
\end{array}
& \quad \begin{array}{c}
R^M \rightarrow R^Y \\
\downarrow \\
M \rightarrow Y \\
\downarrow \\
Y^*
\end{array}
& \quad \begin{array}{c}
R^M \rightarrow R^Y \rightarrow R^{Y*} \\
\downarrow \\
M \rightarrow Y \\
\downarrow \\
Y^*
\end{array}
\end{align*}

(a) \quad (b) \quad (c)
1 Notation and Basic Assumptions

2 Identification under MNAR: missingness only in the mediator

3 Identification under MNAR: missingness both in the mediator and outcome

4 Application to the Job Corps Study

5 Summary
The data describes 8,707 subjects who were randomized to either Job Corps group ($T = 1$) or control group ($T = 0$).

$M$: whether subject obtained an educational/vocational certificate or not (collected at 30-month followup); 1 if obtained a certificate, and 0 otherwise.

$Y$: weekly earnings four years after randomization.

Missingness both in $M$ and in $Y$.

$X$: gender, age, race, education level, earnings in the year before participating in the study, whether the subject had a child or not, and whether the subject had ever been arrested or not.
Use two-part models to address the excessive zero values and skewed positive values of earnings.
Model for $M$: logit $P(M_i = 1|T_i, X_i) = \alpha_0 + \alpha_t T_i + \alpha_x^T X_i$

Model for $Y$: define $Z_i = 0$ if $Y_i = 0$, and $Z_i = 1$ if $Y_i > 0$. Two-part Gamma model for $Y$ with log link:
logit $P(Z_i = 1 | M_i, T_i, X_i) = \delta_0 + \delta_m M_i + \delta_t T_i + \delta_m T M_i \cdot T_i + \delta_x^T X_i$,
$Y_i | Z_i = 1, M_i, T_i, X_i \sim \text{Gamma}(\nu, \nu/\mu_i(M_i, T_i, X_i))$, where
$\mu_i(M_i, T_i, X_i) = \exp(\beta_0 + \beta_m M_i + \beta_t T_i + \beta_m T M_i \cdot T_i + \beta_x^T X_i)$

Model for $R^M$: logit $P(R^M_i = 1|M_i, T_i, X_i) = \lambda_0 + \lambda_m M_i + \lambda_t T_i + \lambda_x^T X_i$

Model for $R^Y$:
Under Assumption II:
logit $P(R^Y_i = 1|R^M_i, T_i, X_i) = \gamma_0 + \gamma_{rM} R^M_i + \gamma_t T_i + \gamma_x^T X_i$;

Under Assumption III:
logit $P(R^Y_i = 1|Z_i, T_i, X_i) = \gamma_0 + \gamma_z Z_i + \gamma_t T_i + \gamma_x^T X_i$;

Under Assumption IV:
logit $P(R^Y_i = 1|M_i, T_i, X_i) = \gamma_0 + \gamma_m M_i + \gamma_t T_i + \gamma_x^T X_i$. 
Model comparison

Table 2: Model comparison among models under MNAR Assumptions II, III and IV using two-part Gamma and log-normal models. The log-likelihoods are evaluated at the corresponding MLEs.

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Model</th>
<th>Log-likelihood</th>
<th>NIE</th>
<th>NDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Gamma</td>
<td>−53131.35 ✓</td>
<td>10.94 (7.94, 14.29)</td>
<td>12.93 (−1.95, 27.64)</td>
</tr>
<tr>
<td>III</td>
<td>Gamma</td>
<td>−53488.54</td>
<td>14.87 (11.59, 18.35)</td>
<td>9.99 (−2.99, 22.73)</td>
</tr>
<tr>
<td>IV</td>
<td>Gamma</td>
<td>−53475.01</td>
<td>10.14 (7.26, 13.25)</td>
<td>11.29 (−3.85, 26.21)</td>
</tr>
<tr>
<td>II</td>
<td>Log-normal</td>
<td>−53799.79</td>
<td>15.50 (11.06, 20.16)</td>
<td>4.14 (−18.14, 26.42)</td>
</tr>
<tr>
<td>III</td>
<td>Log-normal</td>
<td>−54159.23</td>
<td>19.23 (14.79, 23.81)</td>
<td>3.21 (−15.37, 21.74)</td>
</tr>
<tr>
<td>IV</td>
<td>Log-normal</td>
<td>−54145.92</td>
<td>14.36 (10.16, 18.71)</td>
<td>1.68 (−20.82, 24.21)</td>
</tr>
</tbody>
</table>

MNAR Assumption II

MNAR Assumption III

MNAR Assumption IV
Table 3: CI based on 500 bootstrap samples; $\lambda_m$, coefficient of $M$ in the $R^M$ model; $\gamma_{rM}$, coefficient of $R^M$ in the $R^Y$ model.

<table>
<thead>
<tr>
<th></th>
<th>Complete Case</th>
<th></th>
<th>Multiple Imputation</th>
<th></th>
<th>EM Algorithm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
<td>Estimate</td>
<td>95% CI</td>
<td>Estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>$\lambda_m$</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.73</td>
<td>(0.34, 3.33)</td>
</tr>
<tr>
<td>$\gamma_{rM}$</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.87</td>
<td>(1.76, 2.00)</td>
</tr>
<tr>
<td>NIE</td>
<td>12.00</td>
<td>(8.65, 15.57)</td>
<td>12.04</td>
<td>(8.25, 14.60)</td>
<td>10.94</td>
<td>(7.94, 14.29)</td>
</tr>
<tr>
<td>NDE</td>
<td>14.75</td>
<td>(−0.05, 29.50)</td>
<td>9.22</td>
<td>(−5.85, 23.23)</td>
<td>12.93</td>
<td>(−1.95, 27.64)</td>
</tr>
</tbody>
</table>

- The causal conclusions regarding the NIE and NDE are the same among the three methods, in spite of the significant effect of $M \rightarrow R^M$ ($\lambda_m$) and the significant effect of $R^M \rightarrow R^Y$ ($\gamma_{rM}$).
Sensitivity analysis

Missing data mechanism for the sensitivity analysis.

- Revised model for $R^Y$: $\logit P(R^Y = 1 \mid R^M = r^M, Z = z, M = m, T = t, X = x) = \gamma_0 + \gamma_{r^M} r^M + \gamma_z z + \gamma_m m + \gamma_t t + \gamma_x x$, where $\gamma_z$ and $\gamma_m$ are sensitivity parameters.

- When $\gamma_z = \gamma_m = 0$, it is the same as the previous analysis under MNAR Assumption II.
Sensitivity analysis

Table 4: Est, estimate; CI, confidence interval based on 500 bootstrap samples; $\gamma_z$ (sensitivity parameter), coefficient of $Z$ in the $R^Y$ model; $\gamma_m$ (sensitivity parameter), coefficient of $M$ in the $R^Y$ model.

<table>
<thead>
<tr>
<th></th>
<th>$\gamma_m$</th>
<th>$\gamma_z = -2$</th>
<th>$\gamma_z = 0$</th>
<th>$\gamma_z = 2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Est</td>
<td>95% CI</td>
<td>Est</td>
<td>95% CI</td>
</tr>
<tr>
<td>NIE</td>
<td>−2</td>
<td>11.15 (7.97, 14.49)</td>
<td>11.49 (8.24, 14.83)</td>
<td>14.33 (11.02, 17.89)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>11.30 (8.12, 14.58)</td>
<td>10.94 (7.94, 14.29)</td>
<td>13.40 (10.22, 16.78)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>11.39 (8.19, 14.63)</td>
<td>10.83 (7.98, 14.25)</td>
<td>10.48 (7.15, 14.81)</td>
</tr>
<tr>
<td>NDE</td>
<td>−2</td>
<td>13.18 (−1.53, 27.88)</td>
<td>13.90 (−1.00, 28.57)</td>
<td>11.72 (−2.33, 26.34)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>12.82 (−1.90, 27.52)</td>
<td>12.93 (−1.95, 27.64)</td>
<td>11.27 (−3.12, 25.57)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12.50 (−2.24, 27.16)</td>
<td>12.25 (−2.38, 27.33)</td>
<td>15.43 (−0.18, 29.47)</td>
</tr>
</tbody>
</table>

The causal conclusions on the NIE and NDE are not sensitive to a strong impact of $Z \rightarrow R^Y$ and/or $M \rightarrow R^Y$ in addition to the impact of $R^M$ on $R^Y$. 
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4. Application to the Job Corps Study

5. Summary
Show some positive results on nonparametric identification of NIE and NDE when mediator and/or outcome are MNAR.

One of our favorite statistics quotes:

“If an issue can be addressed nonparametrically then it will often be better to tackle it parametrically; however, if it cannot be resolved nonparametrically then it is usually dangerous to resolve it parametrically.”


