Delicatessen: M-Estimation in Python

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October 12, 2022

Abstract

M-estimation is a general statistical framework that simplifies estimation. Here, we introduce delicatessen, an open-source Python library that flexibly automates the mathematics of M-estimation. To highlight the utility of delicatessen for quantitative data analysis, we provide several illustrations common to life science research: linear regression robust to outliers, estimation of a dose-response curve, and standardization of results.

M-estimation is a general large-sample statistical framework [1]. Widespread application of M-estimation is hindered by tedious derivative and matrix calculations. To address this barrier, we developed delicatessen, an open-source Python library that flexibly automates the mathematics of M-estimation. Delicatessen supports both built-in and custom, user-specified estimating equations. To help contextualize the value of M-estimation and delicatessen, we showcase several applications common to statistical analyses in life sciences research: regression with outliers, dose-response curves, and standardization.

To begin, we briefly review M-estimation; see Stefanski and Boos (2002) for a thorough introduction [1]. An M-estimator, \( \hat{\theta} \), is the solution for \( \theta \) to the vector equation \( \sum_{i=1}^{n} \psi(Z_i; \theta) = 0 \), where \( \theta = \{\theta_1, \theta_2, ..., \theta_v\} \) is the parameter vector, \( \psi(.) \) is a \( (v \times 1) \)-dimension estimating equation, and \( Z_i \) are the observed data for \( n \) independent and identically distributed units. As an example, the M-estimator for the mean (\( \mu \)) of a variable (\( Y_i \)) is \( \sum_{i=1}^{n} (Y_i - \mu) = 0 \), which is equivalent to the usual mean estimator, \( \hat{\mu} = n^{-1} \sum_{i=1}^{n} Y_i \). To find \( \hat{\theta} \), root-finding procedures can be used, which iteratively search for the value(s) of \( \hat{\theta} \) where \( \sum_{i=1}^{n} \psi(Z_i; \hat{\theta}) = 0 \). The variance of \( \hat{\theta} \) can be estimated using the empirical sandwich variance estimator (see Appendix). Key advantages of the sandwich estimator are reduced computational burden for variance estimation relative to common alternatives (e.g., bootstrapping [2] [3], Monte Carlo methods [4], etc.), automation of the delta method, and valid variance estimation for parameters that depend on other estimated parameters [1].

M-estimators are implemented in delicatessen via the MEstimator class. Input to MEstimator includes the estimating equation(s) and starting values for the root-finding algorithm. Root-finding algorithms implemented in SciPy [5], as well as custom root-finding algorithms, are supported. After finding \( \hat{\theta} \), the ‘bread’ of the sandwich estimator is calculated by numerically approximating the partial derivatives via the central difference formula and the ‘filling’ of the sandwich is calculated using NumPy [6]. Finally, the sandwich covariance matrix is constructed. While other M-estimation implementations exist [7] [8] [9], delicatessen provides greater support for both user-specified and pre-built estimating equations (Appendix Table 1).

To demonstrate application of delicatessen, we provide three examples common to life sciences research. First, consider linear regression with outliers [10] [11]. A common approach to handling outliers is to exclude them. However, exclusion ignores all information contributed by outliers, and should only be done when outliers are unambiguously a result of experimental error [11]. Yet, including outliers with simple linear regression can lead to unstable or unreliable estimates. Robust regression has been proposed as an alternative, whereby outliers contribute but their influence is curtailed [12] [13]. The estimating equations for the intercept and slope with robust linear regression are

\[
\psi(Y_i, X_i, \alpha) = \begin{bmatrix} f_k(Y_i - (1, X_i)\alpha^T) \alpha \end{bmatrix}
\]

where \( f_k \) is a robust function, and \( \alpha \) is the parameter vector.
where $Y_i$ is the independent variable, $X_i$ is the dependent variable(s), $\alpha = (\alpha_0, \alpha_1)$ is the parameter vector for the regression model, and $f_k(\cdot)$ truncates or bounds the residuals at $-k, k$. To illustrate, 15 observations were simulated following Altman & Krzywinski (2016) [11] and all models were fit using \texttt{delicatessen} with built-in estimating equations. As a reference, a linear model was fit to the simulated data (Figure 1a, original reference simulated following Altman & Krzywinski (2016) [11] and all models were fit using \texttt{delicatessen} the regression model, and $\psi(R_i, D_i; \theta) = \left[ \psi_{PL}(R_i, D_i; \gamma) \psi_{EC}(S_{20}, \gamma) \right]$ where $\theta = (\gamma, \delta_a)$. The variance for $\delta_a$ is automatically estimated through the sandwich. The sandwich variance can then be used to construct Wald-type 95% confidence intervals (CI). The estimated dose-response curve using \texttt{delicatessen} and the built-in estimating equations is shown in Figure 1b. The estimated 20% effective concentration was 1.86 (95% CI: 1.58, 2.14). This example highlights how M-estimation can be used to apply the delta method, with \texttt{delicatessen} automating the process.

Finally, consider the problem of standardization. Often the available data is not a random sample of the population. Consider the biomarker data from a convenience sample of HIV patients ($n = 57$) in Kamat et al. (2012) [17]. When comparing the prevalence of recent drug use (either cocaine or opiates) to a more generalizable cohort,[18] drug use was notably higher in Kamat et al.’s sample (70% versus 8%). As Kamat et al. reported differential biomarker expression by cocaine use, differential patterns in drug use between data sets indicates that the summary statistics on biomarker expression may not be generalizable. To account for the discrepancy, drug use was standardized for select biomarkers using inverse odds weights [19]. Inverse odds weights for the estimating equations

\[
\psi_{\omega}(S_i, X_i, \beta) = \left[ \frac{(S_i - \expit((1, X_i)\beta^T))1}{(S_i - \expit((1, X_i)\beta^T))X_i} \right]
\]
where $X_i$ indicates drug use for individual $i$, $S_i$ indicates if the individual was in the Kamat et al. study ($S_i = 1$) or in the cohort ($S_i = 0$), and $\text{expit}(\cdot)$ is the inverse logit. The estimating equation for the weighted mean is

$$\psi_m(B_i, S_i, \mu_m, \beta) = I(S_i = 1) \times w_i(X_i; \beta) \times (\log(B_i^m) - \mu_m)$$

where $\log(B_i^m)$ is the log-transformed biomarker $m$, $\mu_m$ is the mean for biomarker $m$, and $w_i(X_i; \beta) = (1 - \expit(X_i^T \beta)) / \expit(X_i^T \beta)$ is the inverse odds weight. While $\beta$ is not of primary interest, the estimates of $\mu_m$ depend on $\beta$ through the inverse odds weights. This dependence means that the estimated variance of $\beta$ should carry forward into the estimated variance of $\mu_m$. Ignoring this dependence puts us in danger of underestimating the uncertainty in the means for biomarker expression. M-estimators address this issue via the sandwich, where the uncertainty of parameters are propagated through the stacked estimating equations. Therefore, estimating equations for the logistic model and for the biomarker means were stacked together and $\theta = (\beta, \mu_1, \mu_2, ..., \mu_m)$. The stacked estimating equations were implemented in delicatessen by a combination of built-in and user-specified estimating equations. Results for select biomarkers are presented in Figure 1c. Notably, the means for log-transformed sIL-2R and IL-12 decreased after standardization. While these results were standardized by drug use, definitions varied between studies and other important differences between the populations the samples were drawn from likely exist. Therefore, these results should only be viewed as an illustration of how M-estimation can be used.

To summarize, M-estimation is a flexible framework. To automate the mathematics of M-estimators, we developed delicatessen, which supports both pre-built and user-created estimating equations. Key features of delicatessen were highlighted through examples in life science research. Further examples can be found on our website.

**Acknowledgments**

The authors would like to thank Drs. Michael Love, Adaora Adimora, and trainees on HIV/STI training grant at University of North Carolina at Chapel Hill for their feedback. PNZ was supported by T32-AI007001 at the time of the software development and writing of this paper. All code is available on GitHub (github.com/pzivich/Delicatessen) and through the Python Package Index. Documentation and further examples can be found on GitHub and the project website (deli.readthedocs.io/en/latest/). Feature requests, bug reports, or help requests can be done through the GitHub repository.

**References**

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Appendix

Empirical Sandwich Covariance Estimator

The empirical sandwich variance estimator, $V(Z; \hat{\theta})$, for the asymptotic covariance matrix is

$$B(Z; \hat{\theta})^{-1} F(Z; \hat{\theta}) \left( B(Z; \hat{\theta})^{-1} \right)^T$$

where the ‘bread’ of the sandwich estimator is

$$B(Z; \hat{\theta}) = \frac{1}{n} \sum_{i=1}^{n} \left( -\psi'(Z_i; \hat{\theta}) \right)$$

with $\psi'(Z_i; \hat{\theta})$ indicating the matrix derivative, and the ‘filling’ of the sandwich estimator is

$$F(Z; \hat{\theta}) = \frac{1}{n} \sum_{i=1}^{n} \psi(Z_i; \hat{\theta}) \psi(Z_i; \hat{\theta})^T$$

The finite sample variance estimator is obtained by scaling the asymptotic variance estimate by $n$, $n^{-1} \times V(Z; \hat{\theta})$.

Estimating Equations

The estimating equations for the 3-parameter log-logistic model with a lower dose-response limit of zero are

$$
\psi_{PL}(D_i, R_i, \gamma) = \begin{bmatrix}
2\gamma_3(Y_i - \hat{Y}_i) - \frac{\rho}{\gamma_1 (1 + \rho)^2} \\
2\gamma_3(Y_i - \hat{Y}_i) \log(D_i/\gamma_1) - \frac{\rho}{(1 + \rho)^2} \\
2(Y_i - \hat{Y}_i) - \frac{\rho}{(1 + \rho)^2}
\end{bmatrix}
$$

where $\rho = (D_i/\gamma_1)^{\gamma_2}$ and $\hat{Y}_i = \theta_3/1 + \rho$. The first, second, and third estimating equations are for $\gamma_1$, $\gamma_2$, and $\gamma_3$, respectively. The effective dose estimating equation is

$$
\psi_{EC}(\delta_a, \gamma) = \begin{bmatrix}
\gamma_3 - \gamma_3(1 - a) \left( 1 + \frac{2}{\gamma_1} \right)^{\gamma_2}
\end{bmatrix}
$$

As previously stated, the effective dose estimating equation is a transformation of the 3-parameter log-logistic model parameters (i.e., it does not depend on $D_i$ or $R_i$).
Table 1: Available features of open-source software implementing M-estimation

| Library     | Language | User-Specified EE | Built-in EE |        |        |        |        | IPW | AIPW |
|-------------|----------|-------------------|-------------|--------|--------|--------|--------|-----|------|
| delicatessen| Python   | x                 | x           | x      | x      | x      | x      | x   | x    |
| statsmodels | Python   |                   |             | x      |        |        |        |     |      |
| sklearn     | Python   |                   |             |        |        |        |        |     |      |
| geex        | R        |                   |             |        |        |        |        |     |      |
| sandwich    | R        |                   |             |        | x      |        |        |     |      |
| MASS        | R        |                   |             |        |        |        |        |     |      |
| rlm         | R        |                   |             |        |        |        |        |     |      |
| drc         | R        |                   |             |        |        |        |        |     |      |
| Mestimation | Julia    |                   |             |        |        |        |        |     |      |

EE: estimating equation(s). IPW: inverse probability weighting, AIPW: augmented inverse probability weighting.
* Available features based on most recent version of each software as of 2022/02/13.
1 Delicatessen: M-Estimation in Python

The following is the code to replicate the three examples provided in the paper. Code written by Paul Zivich (last update: 2022/10/03)

```python
# Loading packages for examples
import numpy as np
import scipy as sp
import pandas as pd
import matplotlib
import matplotlib as mpl
import matplotlib.pyplot as plt
%mplinline
mpl.rcParams['figure.dpi'] = 600

import delicatessen
from delicatessen import MEstimator
from delicatessen.data import load_robust_regress, load_inderjit
from delicatessen.estimating_equations import (ee_regression,
                                               ee_robust_regression,
                                               ee_3p_logistic,
                                               ee_effective_dose_delta,
                                               ee_logistic_regression)

from delicatessen.utilities import inverse_logit

decimal_places = 3
np.random.seed(51520837)

print("NumPy version: ", np.__version__)
print("SciPy version: ", sp.__version__)
print("Pandas version: ", pd.__version__)
print("Matplotlib version: ", matplotlib.__version__)
print("Delicatessen version: ", delicatessen.__version__)

NumPy version: 1.19.5
SciPy version: 1.5.4
Pandas version: 1.1.5
Matplotlib version: 3.3.4
```
1.1 Case Study 1: Linear Regression

```python
# Loading the data without the outlier to generate reference
d = load_robust_regress(outlier=False)  # Loads data without outlier
x = d[:, 0]  # Extract X-values (height)
y = d[:, 1]  # Extract Y-values (weight)
X = np.vstack((np.ones(x.shape[0]), x)).T  # Convert to array

def psi_simple_linear(theta):
    """Built-in estimating equation for linear regression."
    return ee_regression(theta=theta,
                         X=X,
                         y=y,
                         model='linear')

# Linear regression without the outlier for reference
lme = MEstimator(psi_simple_linear,
                 init=[0., 0.])
lme.estimate(solver='hybr')

# Loading the data with the outlier
# Loads data with outlier
y = d[:, 1]  # Extract Y with outlier

# Linear regression with the outlier
ulme = MEstimator(psi_simple_linear,
                  init=[0., 0.])
ulme.estimate(solver='hybr')

# Notice: the theta from the previous regression is used since
#   robust regression can fail when initial values are too far.
rlme = MEstimator(psi_case1_robust,
                 init=[ulme.theta])
```

```
init=ulme.theta
rlme.estimate(solver='hybr')

[5]: # Displaying results
plt.figure(figsize=[6, 4])
xlin = np.linspace(159, 170, 100)

# Plotting linear model results
plt.plot(xlin, lme.theta[0] + xlin*lme.theta[1], '--', color='k', label='Before outlier')
plt.plot(xlin, ulme.theta[0] + xlin*ulme.theta[1], '-', color='red', label='After outlier')
plt.plot(xlin, rlme.theta[0] + xlin*rlme.theta[1], '-', color='blue', label='Robust')

# Plotting the data points (including the outlier)
plt.scatter(x, y, s=40, c='gray', edgecolors='k', label=None, zorder=4)
plt.scatter(159.386, y[x == 159.386] - 3, s=50, c='gray', edgecolors='k', zorder=4)
plt.scatter(159.386, y[x == 159.386], s=50, c='red', edgecolors='k', zorder=5)
plt.arrow(159.386, float(y[x == 159.386]) - 2.75, 0, 2.1, head_width=0.2, facecolor='k', zorder=5)

# Making nice labels for graph
plt.xlabel("Height (cm)")
plt.ylabel("Weight (kg)")
plt.legend()

# Outputting result
plt.tight_layout()
1.2 Case Study 2: Dose-Response Curve

[6]: d = load_inderjit()

[7]: def psi(theta):
   # Asserting that the lower limit is zero
   lower_limit = 0

   # Estimating equations for the 3PL model
   pl3 = ee_3p_logistic(theta=theta[0:3],
                        X=d[:, 1], y=d[:, 0],
                        lower=lower_limit)

   # Estimating equations for the effective concentrations
   ed20 = ee_effective_dose_delta(theta[3], y=d[:, 0], delta=0.20,
                                   steepness=theta[0], ed50=theta[1],
                                   lower=lower_limit, upper=theta[2])

   # Returning stacked estimating equations
   return np.vstack((pl3,
                     ed20))
# Optimization procedure
mest = MEstimator(psi, init=[3.3, 2.5, 8., 2.])
mest.estimate(solver='lm', maxiter=2000)

# Printing the results to the console
print("Case Study 2: Results")
print("ED(50)")
print("Est: ", np.round(mest.theta[0], decimal_places))
print("95% CI: ", np.round(ci_theta[0], decimal_places))
print("Steepness")
print("Est: ", np.round(mest.theta[1], decimal_places))
print("95% CI: ", np.round(ci_theta[1], decimal_places))
print("Upper Limit")
print("Est: ", np.round(mest.theta[2], decimal_places))
print("95% CI: ", np.round(ci_theta[2], decimal_places))
print("ED(20)")
print("Est: ", np.round(mest.theta[3], decimal_places))
print("95% CI: ", np.round(ci_theta[3], decimal_places))

Case Study 2: Results
----------------------
ED(50)
----------------------
Est: 3.263
95% CI: [2.743 3.784]
----------------------
Steepness
----------------------
Est: 2.47
95% CI: [1.897 3.043]
Upper Limit
----------------------------------
Est:  7.855
95% CI: [7.554 8.157]
----------------------------------
ED(20)
----------------------------------
Est:  1.862
95% CI: [1.581 2.143]
========================================

[9]: # Displaying results
    plt.figure(figsize=[6, 4])

    x = np.linspace(0, 100, 5000)
    theta = mest.theta
    y = 0 + (theta[2] - 0) / (1 + (x/theta[0])**theta[1])

    # Plotting points and drawing dose-response line
    plt.plot(x, y, '-', color='blue', linewidth=2)
    plt.scatter(d[:, 1], d[:, 0], s=40, c='gray', edgecolors='k', zorder=5)

    plt.ylim([0, 9])
    plt.xlabel("Root length (cm)")
    plt.xscale('symlog', linthresh=0.3)
    plt.xlim([-0.02, 100])
    plt.xticks([0, 1, 10, 30, 100],
               ["0", "1", "10", "30", "100"])
    plt.xlabel("Ferulic acid (mM)"
    plt.tight_layout()
1.3 Case Study 3: Standardization to external population

```python
# Loading Kamat et al. 2012
d1 = pd.read_csv("data/kamat.et.al.2012_biomarkers.csv")
d1['drug_use'] = np.where(d1['Cocaine'] + d1['Opiate'] > 0, 1, 0)
d1['S'] = 1
biomarkers = ['IFN_alpha', 'CXCL9', 'CXCL10', 'sIL-2R', 'IL12']
d1 = d1[['drug_use', 'S', ] + biomarkers].copy()
for bm in biomarkers:
    d1[bm] = np.log(d1[bm])

# MACS/WIHS in 2018-2019 of cocaine or heroin use in previous 6 months

d0 = pd.DataFrame()
d0['drug_use'] = [1]*300 + [0]*(4016-300)
d0['S'] = 0

# Stacking data together and adding constant for model

d = pd.concat([d0, d1])  # Stacking data sets together
d['constant'] = 1         # Creating intercept for the model
d[biomarkers] = d[biomarkers].fillna(9999)
```
def psi_standard_mean(theta):
    # Returning stacked estimating equations
    return (np.asarray(d1['IFN_alpha']) - theta[0],
            np.asarray(d1['CXCL9']) - theta[1],
            np.asarray(d1['CXCL10']) - theta[2],
            np.asarray(d1['sIL-2R']) - theta[3],
            np.asarray(d1['IL12']) - theta[4],
            )

nm = MEstimator(psi_standard_mean, init=[1.,]*5)
nm.estimate()

# Weighted means to standardize to population
x = np.asarray(d[['constant', 'drug_use']])
s = np.asarray(d['S'])

def psi_weighted_mean(theta):
    global x, y, s
    # Estimating weights
    nuisance = ee_logistic_regression(theta=theta[:2],
                                       X=x, y=s)
    pi = inverse_logit(np.dot(x, theta[:2]))
    weight = np.where(s == 1, (1-pi)/pi, 0)

    # Returning stacked estimating equations
    return np.vstack((nuisance,
                       s*weight*(np.asarray(d['IFN_alpha']) - theta[2]),
                       s*weight*(np.asarray(d['CXCL9']) - theta[3]),
                       s*weight*(np.asarray(d['CXCL10']) - theta[4]),
                       s*weight*(np.asarray(d['sIL-2R']) - theta[5]),
                       s*weight*(np.asarray(d['IL12']) - theta[6]),
                       ))

wm = MEstimator(psi_weighted_mean, init=[0, 0] + [1.,]*5)  
wm.estimate()

# Displaying results
plt.figure(figsize=[6, 4])

# Plotting point estimates
plt.scatter(nm.theta, [i-0.2 for i in range(len(biomarkers))],
            s=40, color='red', edgecolors='k', marker='D',
            zorder=3, label='Naive')
plt.scatter(wm.theta[2:], [i+0.2 for i in range(len(biomarkers))],
            color='black', edgecolors='k', marker='D',
            zorder=3, label='Weighted')
plt.legend()
# Plotting confidence intervals
plt.hlines([i-0.2 for i in range(len(biomarkers))],
    nm.theta - 1.96*np.diag(nm.variance)**0.5,
    nm.theta + 1.96 * np.diag(nm.variance)**0.5,
    colors='red')
plt.hlines([i+0.2 for i in range(len(biomarkers))],
    wm.theta[2:] - 1.96*np.diag(wm.variance)[2:]**0.5,
    wm.theta[2:] + 1.96 * np.diag(wm.variance)[2:]**0.5,
    colors='blue')

# Some shaded regions to make it easier to examine
plt.fill_between([3, 7.5], [3.5, 3.5], [2.5, 2.5], color='gray', alpha=0.1)
plt.fill_between([3, 7.5], [1.5, 1.5], [0.5, 0.5], color='gray', alpha=0.1)
plt.yticks([i for i in range(len(biomarkers))],
    ['IFN-α', 'CXCL9', 'CXCL10', 'sIL-2R', 'IL-12'])
plt.ylim([4.5, -0.5])
plt.xlim([3.5, 7.5])
plt.xlabel("Mean of log-transformed biomarkers")
plt.legend()
plt.tight_layout()
This concludes the examples.

1.4 References

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