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Disclaimer: views are ours and not those of NIH, DHHS, US government

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Run Code

- github.com/pzivich/ABCs_of_M-estimation
 - Open your preferred statistical software
 - Open corresponding mean.* script
 - Run the full script

```
Closed-form: 8.0
Root-finder: 8.0
95% CI: [ 0.8, 15.2]
```

Overview

A Terminological Note

Framework covered today goes by many names

- Estimating Equations
- M-estimation
- Z-estimation

May use terms interchangeably

Learning estimating equations during my postdoc fundamentally changed how I think about and do epidemiology

Approach problems from a different perspective

Made my work simpler by

- Making it easier to construct novel estimators
- Simplifying variance estimation¹
- Being better equipped to read more theoretical papers
- Giving me a tool set to prove statistical properties

¹I almost never use the bootstrap anymore!

Metrika

https://doi.org/10.1007/s00184-024-00962-4



Variance estimation for average treatment effects estimated by g-computation

Stefan Nygaard Hansen¹ • Morten Overgaard¹

Received: 3 February 2023 / Accepted: 8 March 2024 © The Author(s) 2024

Assume now that an estimator $\hat{\beta}_n(\mathbf{z})$ of $\dot{\beta}(\mathbf{z})$ exists for all \mathbf{z} . The asymptotic covariance matrix of Theorem 2 may then be estimated by the following plug-in estimator

$$\hat{\boldsymbol{\Gamma}}_{n}^{\mathbf{a}} = \frac{1}{n} \sum_{i=1}^{n} \left\{ \boldsymbol{\mu}(\hat{\boldsymbol{\beta}}_{n}; \mathbf{X}_{i}^{\mathbf{a}}) - \hat{\boldsymbol{\theta}}_{n}^{\mathbf{a}} + \left(\frac{1}{n} \sum_{j=1}^{n} \frac{\partial}{\partial \boldsymbol{\beta}} \boldsymbol{\mu}(\hat{\boldsymbol{\beta}}_{n}; \mathbf{X}_{j}^{\mathbf{a}}) \right) \hat{\boldsymbol{\beta}}_{n}(\mathbf{Z}_{i}) \right\}^{\otimes 2}$$
(8)

where $\mathbf{x}^{\otimes 2} = \mathbf{x}\mathbf{x}^T$ for a column vector \mathbf{x} .

Under some mild regularity conditions on the estimator $\hat{\beta}_n$, this plug-in estimator will be consistent for the asymptotic covariance matrix as the following result shows.

Theorem 3 Make the assumptions of Theorem 2 and assume furthermore that $\hat{\beta}_n$ satisfies

$$\|\hat{\hat{\boldsymbol{\beta}}}_{n}(\mathbf{z}) - \dot{\boldsymbol{\beta}}(\mathbf{z})\| \le g_{n} \cdot f(\mathbf{z}) \tag{9}$$

for a sequence of random variables $g_n \stackrel{P}{\to} 0$ and a measurable function f with $E(f(\mathbf{Z})^2) < \infty$. Then $\hat{\Gamma}_n^a \stackrel{P}{\to} \Gamma^a$.

Proof See the Appendix.

As an alternative to the two-step approach of this paper, one could consider formulating the two steps as two estimating equations and use (stacked) M-estimation. The sandwich variance estimator from the stacked M-estimation approach corresponds to the variance estimator of this paper. This M-estimation approach has been implemented in the Python library delicatessen as pointed out by a reviewer.

Estimating Equations Use-Cases

Causal inference

- Reifeis et al. (2020) 'Assessing exposure effects on gene expression' Genetic Epidemiology
- Tchetgen Tchetgen et al. (2024) 'Universal difference-in-differences for causal inference in epidemiology' Epidemiology
- Zivich et al. (2023) 'Introducing proximal causal inference for epidemiologists' American Journal of Epidemiology
- Zivich et al. (2023) 'Empirical sandwich variance estimator for iterated conditional expectation g-computation' arXiv:2306.10976

Sensitivity analysis

- Cole et al. (2023) 'Higher-order evidence' European Journal of Epidemiology
- Cole et al. (2023) 'Sensitivity analyses for means or proportions with missing outcome data' Epidemiology

Measurement error

- Boe et al. (2024) 'Practical Considerations for Sandwich Variance Estimation in 2-Stage Regression Settings' American Journal of Epidemiology
- Ross et al. (2024)'Leveraging External Validation Data: The Challenges of Transporting Measurement Error Parameters' Epidemiology

Estimating Equations Use-Cases

Target trial emulation

 DeMonte et al. (2024) 'Assessing COVID-19 Vaccine Effectiveness in Observational Studies via Nested Trial Emulation' arXiv:2403.18115

Generalizability / transportability

- Dahabreh, et al. (2020) 'Extending inferences from a randomized trial to a new target population' Statistics in Medicine
- Dahabreh, et al. (2023) 'Sensitivity analysis using bias functions for studies extending inferences from a randomized trial to a target population' Statistics in Medicine
- Robertson et al (2024) 'Estimating subgroup effects in generalizability and transportability analyses' American Journal of Epidemiology

Data fusion

- Cole et al. (2023) 'Illustration of 2 fusion designs and estimators' American Journal of Epidemiology
- Shook-Sa et al. (2024) 'Fusing trial data for treatment comparisons: single versus multi-span bridging' Statistics in Medicine

Estimating Equations Use-Cases



Pausal Zivference

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For 2025, I am going to do something a bit different. Every Monday is now #MEstimatorMonday

Each Monday, I'll talk about different M-estimators or some of their properties. This 1/52, which will just be some table setting

5 reposts 17 likes

Overview

Section 1: introduction

Break (15min)

Section 2: applied examples

Break (15min)

Section 3: in context

Overview

Section 1: introduction

Break (15min)

Section 2: applied examples

Break (15min)

Section 3: in context

Overview: Section 1

Review notation / definitions

Estimating equations by-hand

Estimating equations with a computer

Some statistical properties

Notation

Review notation and mathematical operations used

- If unfamiliar with something, don't worry!
- Operations will be
 - Contextualized in following sections
 - Mainly done by the computer
- Resource for you to return to later

What we need:

- Basics
- Matrix algebra
- Derivatives

Notation – Basics

 O_i : observed data for unit i

$$\bullet$$
 $O_i = (X_i, Y_i)$

$$\sum_{i=1}^{n} i = 1+2+...+n$$
: cumulative sum

$$\prod_{i=1}^{n} i = 1 \times 2 \times ... \times n$$
: cumulative product

$$\mathsf{expit}(a) = 1/(1 + \exp(-a))$$

E[X]: expected value function

Notation – Basics

estimand (parameter of interest)





estimator



150g unsalted butter, plus extra for greasing 150g plain chocolate, broken into pieces 150g plain flour

1/6 tsp baking powder 1/6 tsp bicarbonate of soda 200g light muscovado sugar Method

Heat the oven to 160C/140C fanigas 3. Grease and base line a 1 life heatproof glass pudding basin and a 450g loaf tin with baking parchment.

 Put the butter and chocolate into a saucepan and melt over a low heat, strning. When the chocolate has all melted remove from the heat.

estimate 0.5



2

 $^{^2}$ Estimand also commonly denoted by θ_0 or θ^*

Notation – Vectors & Matrices

Vector: a list of numbers (or scalars)

$$A = \begin{bmatrix} x \\ y \\ z \end{bmatrix}$$

Matrix: a table of numbers

$$\mathbf{B} = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

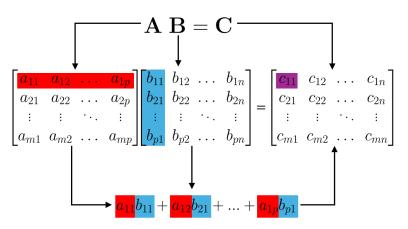
Notation - Matrix Algebra

Transpose

$$\mathbf{A} = egin{bmatrix} a & b \ c & d \ e & f \end{bmatrix} \quad \mathbf{A}^T = egin{bmatrix} a & c & e \ b & d & f \end{bmatrix}$$

Notation - Matrix Algebra

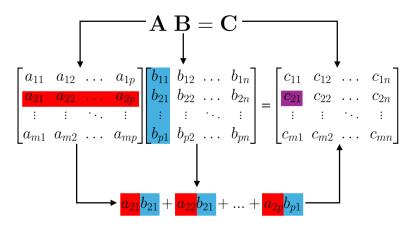
Dot product (matrix multiplication)



 Number of rows in first matrix must match columns in the second matrix

Notation - Matrix Algebra

Dot product (matrix multiplication)



 Number of rows in first matrix must match columns in the second matrix

Notation – Matrix Algebra³

Inverse of 2×2 matrix

$$\mathbf{D} = \begin{bmatrix} w & x \\ y & z \end{bmatrix} \quad \mathbf{D}^{-1} = \frac{1}{w \ z - x \ y} \begin{bmatrix} z & -y \\ -x & w \end{bmatrix}$$

Matrix must have same number of rows and columns

³I've never taken a linear algebra course, so don't worry if this matrix algebra isn't something you're familiar with

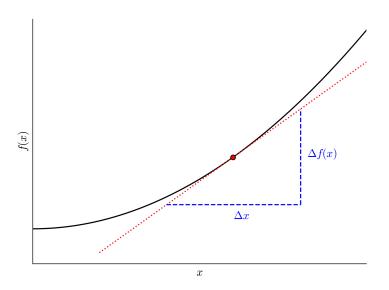
Derivatives - Basics

$$f'(x) = \frac{d}{dx}f(x)$$

Helpful to think of derivative as slope of tangent line at a point

$$f'(x) = \lim_{h \to 0} \frac{f(x+h) - f(x)}{h}$$

Derivatives - Basics



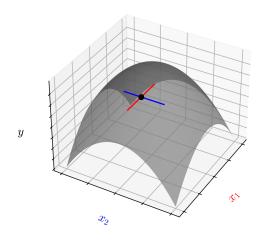
Derivatives – Generalizations

If $m{x}=(x_1,x_2,...,x_m)$ and $f(m{x})=y$, then the partial derivative is $\frac{\partial}{\partial x_1}f(m{x})$

The gradient is

$$abla f(oldsymbol{x}) = egin{bmatrix} rac{\partial}{\partial x_1} f(oldsymbol{x}) \ rac{\partial}{\partial x_2} f(oldsymbol{x}) \ dots \ rac{\partial}{\partial x_m} f(oldsymbol{x}) \end{bmatrix}$$

Derivatives – Generalizations



Derivatives – Generalizations

The Hessian is

$$\Delta H_f(\boldsymbol{x}) = \begin{bmatrix} \frac{\partial^2}{\partial x_1 \partial x_1} f(\boldsymbol{x}) & \dots & \frac{\partial^2}{\partial x_1 \partial x_m} f(\boldsymbol{x}) \\ \vdots & \ddots & \vdots \\ \frac{\partial^2}{\partial x_m \partial x_1} f(\boldsymbol{x}) & \dots & \frac{\partial^2}{\partial x_m \partial x_m} f(\boldsymbol{x}) \end{bmatrix}$$

ullet Jacobian (transpose gradient, $abla^T$) of the gradient

Derivatives - Generalization

Function

$$f(x_1, x_2) = y$$

Gradient

$$\nabla f(x_1, x_2) = \begin{bmatrix} \frac{\partial}{\partial x_1} f(x_1, x_2) \\ \frac{\partial}{\partial x_2} f(x_1, x_2) \end{bmatrix}$$

Hessian

$$\Delta H_f(\boldsymbol{x}) = \begin{bmatrix} \frac{\partial^2}{\partial x_1 \partial x_1} f(x_1, x_2) & \frac{\partial^2}{\partial x_1 \partial x_2} f(x_1, x_2) \\ \frac{\partial^2}{\partial x_2 \partial x_1} f(x_1, x_2) & \frac{\partial^2}{\partial x_2 \partial x_2} f(x_1, x_2) \end{bmatrix}$$

Notation - Estimating Equations

Estimating function

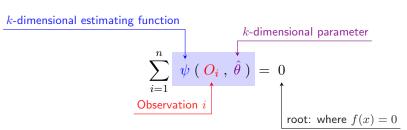
$$\psi(O_i;\theta)$$

Estimating equation

$$\sum_{i=1}^{n} \psi(O_i; \theta)$$

Estimator

Our estimator, $\hat{\theta}$, is the solution to



Example 0: the mean

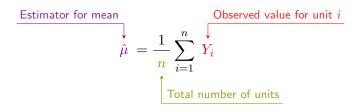
Problem: Learn the Mean

Want to learn the population mean

• Estimand: $\mu = E[Y]$

Suppose we have the following observations to estimate μ

Usual method



Applying to data in example (estimate)

$$\frac{7+1+5+3+24}{5} = \frac{40}{5} = 8$$

but let's use estimating equations instead

An Algorithm for Estimating Equations

- 1. Determine estimating function
- 2. Find the roots of the estimating equations
- 3. Estimate variance via the sandwich

1. Determine Estimating Function

Goal: rewrite mean as a function that is equal to zero

$$\hat{\mu} = \frac{1}{n} \sum_{i=1}^{n} Y_{i} \qquad \text{def'n}$$

$$\hat{\mu} \quad n = \sum_{i=1}^{n} Y_{i} \qquad \text{multiply by } n$$

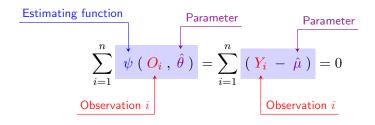
$$0 = \left(\sum_{i=1}^{n} Y_{i}\right) - \hat{\mu} \quad n \qquad \text{subtract } \hat{\mu}n$$

$$0 = \left(\sum_{i=1}^{n} Y_{i}\right) - \left(\sum_{i=1}^{n} \hat{\mu}\right) \quad \text{def'n of } \times$$

$$0 = \sum_{i=1}^{n} (Y_{i} - \hat{\mu}) \qquad \text{associativity}$$

1. Determine Estimating Function

This formula is the estimating equation of the mean

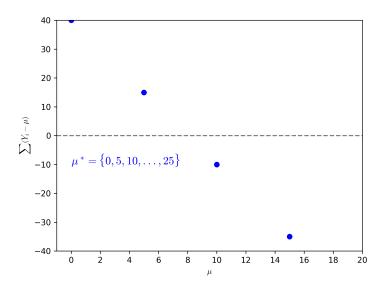


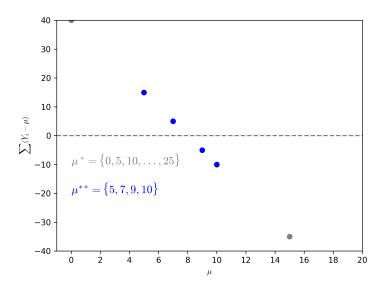
How can we find $\hat{\mu}$?

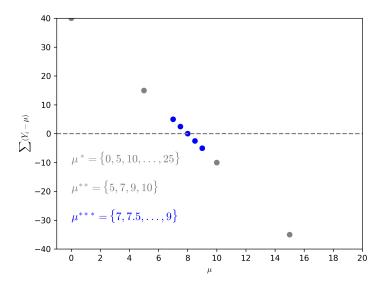
• Ignore the closed-form solution for the time

Broadly

- 1. Take some guesses at $\;\hat{\mu}$, denoted as $\;\hat{\mu}^*$
- 2. Compute $\sum_{i=1}^{n} \psi(O_i; \hat{\mu}^*)$
- 3. Find the guesses that are close to zero
- 4. Generate some new guesses, $\hat{\mu}^{**}$
- 5. Repeat 2-4 until we find $\,\hat{\mu}$







3. Variance

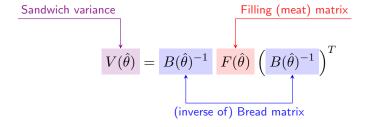
Closed-form estimator⁴

$$\widehat{Var}(\widehat{\mu}) = \frac{1}{n} \sum_{i=1}^{n} (Y_i - \widehat{\mu})^2$$

but let's rely on estimating equations instead

 $^{^4\}mathrm{Note}\colon$ n is often replaced by n-1 in practice, which can lead to differences for small sample sizes

3. Sandwich Variance Estimator



3. Sandwich Variance Estimator

$$\boxed{B(\hat{\theta}) = \frac{1}{n} \sum_{i=1}^{n} \left[-\psi'(O_i, \hat{\theta}) \right]}$$
 Partial derivatives (Jacobian)

Filling matrix
$$F(\hat{\theta}) = \frac{1}{n} \sum_{i=1}^{n} \left[\psi(O_i, \hat{\theta}) \middle| \psi(O_i, \hat{\theta})^T \right]$$
 Dot product of estimating functions

Baking the Bread: By-Hand

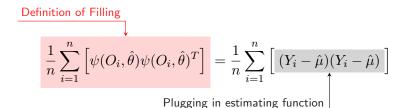
Need the derivative of $\psi(O_i; \mu)$

$$\begin{split} \psi'(O_i;\hat{\mu}) = & \frac{\partial}{\partial \hat{\mu}} \psi(O_i;\hat{\mu}) \quad \text{def'n} \\ = & \frac{\partial}{\partial \hat{\mu}} (Y_i - \hat{\mu}) \quad \text{def'n of estimating function} \\ = & -1 \qquad \qquad \text{derivative rules} \end{split}$$

Therefore

$$\frac{1}{n}\sum_{i=1}^n\left[-\psi'(O_i,\hat{\theta})\right] = \frac{1}{n}\sum_{i=1}^n\left[-\frac{1}{n}\right] = 1$$
 Prom derivative above

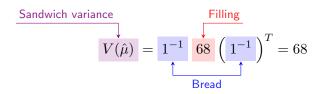
Cooking the Filling: By-Hand



Therefore

$$\frac{1}{5} \sum_{i=1}^{5} \left[(Y_i - 8)^2 \right] = 68$$

Assembling the Sandwich: By-Hand



Wald-type confidence intervals

$$\hat{\mu} \pm z_{\alpha} \sqrt{\frac{V(\hat{\mu})}{n}} = 8 \pm 1.96 \sqrt{\frac{68}{5}} = (0.8, 15.2)$$

Computation of Estimating Equations

Computation of Estimating Equations

Solved estimating equation by-hand

By-hand is not needed

Consider how estimating equations can be implemented algorithmically

- Root-finding
- Approximation of derivatives
- Matrix algebra

Follow along in mean.R, mean.sas, or mean.py

Start of code inputs data and sets up estimating equations

Root-Finding – Algorithms

Performed a by-hand search for $\hat{\mu}$

• Similar to the bisection method

Variety of multidimensional root-finding algorithms exist⁵

- Secant method (quasi-Newton)
- Levenberg-Marquardt
- Powell hybrid method

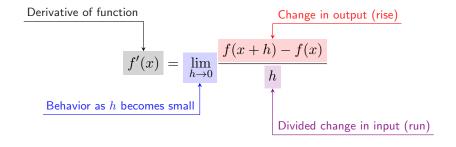
⁵I've found Levenberg-Marquardt to be reliable for most problems

Root-Finding – Code

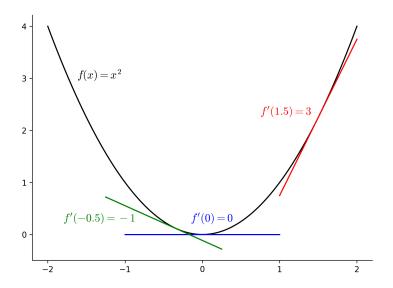
Under <a>Root-finding see implementation

- SAS nlplm
- R rootSolve::multiroot
- Python scipy.optimize.root

Derivatives – Back to the Definition

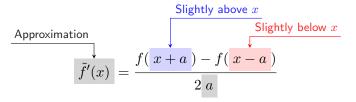


Derivatives – Intuition



Derivatives – Numerical Approximation

Central Difference Method⁶



Here a is a small value (e.g., 1×10^{-9})

 $^{^6}$ Automatic differentiation, which computes exact derivative, could be used instead. But this is not available in all software and is not straightforward to implement by-hand

Baking the Bread - Code

Under **Baking** the bread see implementation

- SAS nlpfdd
- R numDeriv::jacobian
- Python scipy.optimize.approx_fprime

Cooking the Filling – Code

Under Cooking the filling see implementation

- Transpose
 - SAS '
 - R base::t
 - Python numpy.transpose
- Dot product
 - SAS *
 - R %*%
 - Python numpy.dot

Assembling the Sandwich – Code

Under Assembling the sandwich see implementation

- Inverse
 - SAS inv
 - R base::solve
 - Python numpy.linalg.inv

Implications of our Algorithm

To evaluate estimating equations, we only need to provide

- Valid estimating functions
- Data

Everything else can be done by the computer

- Simplify complex analyses
- Open-source libraries
 - R: geex⁷
 - Python: delicatessen⁸

⁷Saul & Hudgens (2020) Journal of Statistical Software

⁸Zivich et al. (2022) arXiv:2203.11300

Extensions

But Why Estimating Equations?

All we've done is calculate the mean in a complicated way

So why bother with estimating equations?

Flexibility of the framework

How Estimating Equations are extended

As will be seen in the next section

- 1. Stacking estimating functions
- 2. Automation of delta method

Stacking estimating functions

Often want to estimate more than 1 parameter

- Regression models
- Effect measure modification
- Inverse probability weighting

Stacking Estimating Functions

Stack estimating functions into a vector

$$\sum_{i=1}^{n} \begin{bmatrix} \psi_{\theta_1}(O_i; \hat{\theta}) \\ \psi_{\theta_2}(O_i; \hat{\theta}) \\ \vdots \\ \psi_{\theta_k}(O_i; \hat{\theta}) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = \mathbf{0}$$

- Easy to stack together
- Unlike maximizing a likelihood
 - Likelihood has a single value for individual contribution
 - More difficult to combine likelihood functions

Stacking Estimating Functions

Example

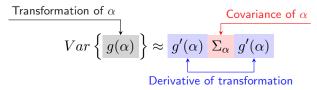
$$\sum_{i=1}^{n} \begin{bmatrix} \psi_{\theta_1}(O_i; \theta) \\ \psi_{\theta_2}(O_i; \theta) \end{bmatrix} = \sum_{i=1}^{n} \begin{bmatrix} Y_i - \theta_1 \\ (Y_i - \theta_1)^2 - \theta_2 \end{bmatrix} = \mathbf{0}$$

- Allow parameter to depend on others
- Concept explored further in applications

Delta Method

Theorem: smooth function of an asymptotically normal estimator is also asymptotically normal⁹

Application:



⁹Boos & Stefanski Essential Statistical Inference pg. 237-240

Delta Method

Many variance formulas you know are Delta method results

- Var(RD), $Var(\log(RR))$, $Var(\log(OR))$
- Formulas follow from Delta method argument
- Don't need to manually solve due to known formulas
 - Not always the case

Delta Method with the Sandwich

The estimating function for the transformed parameter, θ_t is

$$\psi_{g(\theta)}(O_i; \theta, \theta_t) = g(\theta) - \theta_t$$

Estimating function does not depend on data

Therefore, the stacked estimating equations are

$$\sum_{i=1}^{n} \begin{bmatrix} \psi^*(O_i; \theta) \\ \psi_{g(\theta)}(O_i; \theta, \theta_t) \end{bmatrix} = 0$$

Delta Method with the Sandwich

Following some derivatives and matrix algebra

$$V(\theta, \theta_t) = \begin{bmatrix} V^*(\theta) & g'(\theta)V^*(\theta) \\ V^*(\theta)g'(\theta)^T & g'(\theta)V^*(\theta)g'(\theta) \end{bmatrix}$$

where

$$V(\theta_t) = \begin{matrix} g'(\theta) & V^*(\theta) \\ \end{matrix} \begin{matrix} g'(\theta) \end{matrix} \begin{matrix} g'(\theta) \end{matrix}$$
Derivative of transformation

Automate the Delta method!

Robust Variance

To close this section, let's discuss the robust variance

- The sandwich variance is also known as the 'robust' variance
- 'Robust' designates that the variance estimator is not sensitive to violations of certain assumptions¹⁰
 - Variance estimator is consistent when parametric model is wrong
 - However this has some difficulties
- Relates back to Maximum Likelihood Estimation
 - The variance can be estimated two ways

 $^{^{10}}$ See Mansournia et al. (2021) International Journal of Epidemiology for further details

Robust Variance

Variance estimators

- 1 Inverse Hessian of the log-likelihood
 - Equivalent to $B(\theta)^{-1}$
- 2 Residuals of the score function
 - Equivalent to $F(\theta)^{-1}$
- When the model is correctly specified
 - These variance estimators asymptotically equivalent
 - $B(\theta) = F(\theta)$

Robust Variance

When the model is not correctly specified

- $B(\theta) \neq F(\theta)$
- By combining, sandwich is robust to assumptions
 - Variance estimator is consistent even if model is wrong
- Example: log-Poisson model to estimate the risk ratio
 - Here, estimated variance is too large

$Warning^{11}$

• Does not correct for bias in parameter estimates

¹¹See Freedman DA Am Stat 2006 for details

Overview

Section 1: introduction

Break (15min)

Section 2: applied examples

Break (15min)

Section 3: in context