Numerical Integration with an application to Sample size re-estimation

Adrian Mander and Jack Bowden

MRC Biostatistics Unit Hub for Trials Methodology Research

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Outline

- Give a brief introduction to quadrature
- Describe the Stata command and MATA function
  - how to use these for simple integrals
- Numerical difficulties
- Apply it to a harder problem of sample size re-estimation
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Quadrature

Quadrature is another name for **numerical integration**, which is essentially transforming integration into a summation

\[
\int_a^b W(x)f(x) \, dx \approx \sum_{j=0}^{N-1} w_j f(x_j),
\]

where \( w_j \) are weights and \( x_j \) are the abscissas.

- Functions \( W(x) \) are chosen for the appropriate interval \([a, b]\)
- the corresponding \( w_j \) and \( x_j \) values are found using orthogonal polynomials (defined by recurrence functions)
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- Functions $W(x)$ are chosen for the appropriate interval $[a, b]$
- the corresponding $w_j$ and $x_j$ values are found using orthogonal polynomials (defined by recurrence functions)
Common forms of the weight function

Only considered three $W(x)$ functions over three ranges

1. $[-1,1]$ — Gauss-Legendre quadrature, $W(x) = 1$
2. $[0,\infty]$ — Gauss-Lageurre quadrature, $W(x) = \exp(-x)$
3. $[-\infty,\infty]$ — Gauss-Hermite Quadrature, $W(x) = \exp(-x^2)$

All of these methods have been implemented in a Stata command `integrate` available on SSC.

Most of the calculation are written in MATA and uses the trick from Bill Gould to pass functions from Stata to Mata.
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Most of the calculation are written in MATA and uses the trick from Bill Gould to pass functions from Stata to Mata.
How to find the weights/abscissas

The roots of the **Legendre polynomial** defined by

\[
\begin{align*}
P_0(x) &= 1 \\
P_1(x) &= x \\
(n + 1)P_{n+1}(x) &= (2n + 1)xP_n(x) - nP_{n-1}(x)
\end{align*}
\]

are the **abscissas**.

- Finding the roots say using `polyroots()` has limited precision of the machine.
- Golub and Welch solution was to construct a **similarity matrix**
How to find the weights/abscissas

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\[ (n + 1)P_{n+1}(x) = (2n + 1)xP_n(x) - nP_{n-1}(x) \]

are the abscissas.

- Finding the roots say using \texttt{polyroots()} has limited precision of the machine.
- Golub and Welch solution was to construct a \textit{similarity} matrix
Similarity Matrix corresponding to Legendre polynomial

\[
\begin{pmatrix}
0 & \frac{1}{\sqrt{4*1^2-1}} & 0 & \frac{2}{\sqrt{4*2^2-1}} & \cdots & \cdots & \frac{n-1}{\sqrt{4*(n-1)^2-1}} & 0 \\
\frac{1}{\sqrt{4*1^2-1}} & 0 & \frac{2}{\sqrt{4*2^2-1}} & \cdots & \cdots & \cdots & \frac{n-1}{\sqrt{4*(n-1)^2-1}} & 0 \\
0 & \frac{2}{\sqrt{4*2^2-1}} & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\
\frac{2}{\sqrt{4*2^2-1}} & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\
\cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\
\cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\
\frac{n-1}{\sqrt{4*(n-1)^2-1}} & \cdots & \cdots & \cdots & \cdots & \cdots & 0 & \frac{n-1}{\sqrt{4*(n-1)^2-1}} \\
0 & \frac{n-1}{\sqrt{4*(n-1)^2-1}} & \cdots & \cdots & \cdots & \cdots & \frac{n-1}{\sqrt{4*(n-1)^2-1}} & 0
\end{pmatrix}
\]

The eigenvalues are the abscissas and the eigenvectors are used to find the weights.

Hermite polynomial with \( n > 60 \) gives the wrong answers using eigensystem() function.
Similarity Matrix corresponding to Legendre polynomial

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\begin{pmatrix}
0 & \frac{1}{\sqrt{4*1^2-1}} & \frac{2}{\sqrt{4*2^2-1}} & \cdots & \frac{n-1}{\sqrt{4*(n-1)^2-1}} \\
\frac{1}{\sqrt{4*1^2-1}} & 0 & \frac{2}{\sqrt{4*2^2-1}} & \cdots & 0 \\
\frac{2}{\sqrt{4*2^2-1}} & \frac{2}{\sqrt{4*2^2-1}} & \cdots & \cdots & \frac{2}{\sqrt{4*2^2-1}} \\
\ldots & \ldots & \ldots & \ldots & \ldots \\
\frac{n-1}{\sqrt{4*(n-1)^2-1}} & 0 & \frac{2}{\sqrt{4*2^2-1}} & \cdots & 0 \\
\end{pmatrix}
\]

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Hermite polynomial with \( n > 60 \) gives the wrong answers using eigensystem() function.
Basic syntax

To calculate the following expression

\[ \int_{a}^{b} f(x) \, dx \]

In **Stata**

`integrate, function( f(x) ) lower(a) upper(b)`

In **Mata** if the function `f()` already exists then the function address is passed to `integrate`

`integrate(&f(), a, b)`

- \(-\infty\) is specified by setting `a = .`
- similarly, if `b = .` then the upper limit is \(\infty\)
Basic syntax

To calculate the following expression

\[ \int_{a}^{b} f(x) \, dx \]

In Stata

`integrate, function( f(x) ) lower(a) upper(b)`

In Mata if the function `f()` already exists then the function address is passed to integrate

`integrate(&f(), a, b)`

- $-\infty$ is specified by setting $a = .$
- similarly, if $b = .$ then the upper limit is $\infty$
Simple example - Stata

\[ \int_{0}^{3} x^2 \, dx \]  

Using the Stata command

\texttt{integrate, f(x:^2) l(0) u(3)}

Note: The function to be integrated will be compiled using Mata and stored in your personal directory \texttt{~/ado/personal/} (make sure this is writeable)

The integral = 9

Could have done

\texttt{integrate, f(x^2) l(0) u(3) vectorise}
Simple example - Stata

\[ \int_{0}^{3} x^2 \, dx \quad (1) \]

Using the Stata command

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Simple example - Mata

First define the integrand as a new function, the function must return a row vector and the variable of integration must be a rowvector.

```mata
real rowvector f(real rowvector x)
{
    return(x:^2)
}
```

Then to integrate this function type with Mata

```mata
: integrate(&f(), 0, 3)
4
```

All the examples from now on will be based only on the Mata function. Which is available via SSC, integrate.mata contains a do file to compile the mata code.
Mata syntax

The syntax of the Mata function

```
real scalar integrate(&function(), real scalar lower, 
    real scalar upper |, real scalar quadpts, 
    real rowvector xarg)
```

has optional arguments for number of quadrature points and a rowvector of additional arguments that are passed to the function()

- Note that integrate returns a real scalar
Mata syntax

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real scalar integrate(&function(), real scalar lower, real scalar upper |, real scalar quadpts, real rowvector xarg)

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Double Integration

\[ \int_{0}^{1} \int_{0}^{1} (x + y) \, dx \, dy \]

Want to just write
\[ \text{integrate( integrate(&f(),0,1) ,0,1) } \]

- However integrate() does not return a rowvector so this syntax would fail
Double Integration

\[ \int_0^1 \int_0^1 x + y \, dx \, dy \]

Want to just write
\begin{verbatim}
integrate( integrate(&f(),0,1) ,0,1)
\end{verbatim}

- However `integrate()` does not return a rowvector so this syntax would fail
Solution

First define

```plaintext
real rowvector fxy(real rowvector x, real rowvector y)
{
    return(x:+y)
}
```

```plaintext
real rowvector f_inner(real rowvector y)
{
    for(i=1; i<=cols(y);i++) {
        if (i==1) f=integrate(&fxy(), 0, 1, 40, y[i])
        else f = f, integrate(&fxy(), 0, 1, 40, y[i])
    }
    return(f)
}
```

```plaintext
integrate(&f_inner(), 0, 1)
```

1
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    }
    return(f)
}

: integrate(&f_inner(), 0, 1)
1
```
Further Double Integration

\[ \int_{0}^{2} \int_{0}^{y^2} 6xy \, dx \, dy \]

This is also a simple extension to the previous code.
Solution

```plaintext
real rowvector fxy2(real rowvector x, real rowvector y) {
  return(6:*x:*y)
}

real rowvector f_inner2(real rowvector y) {
  for(i=1; i<=cols(y); i++) {
    if (i==1) f=integrate(&fxy2(), 0, y[i]^2, 40, y[i])
    else f = f, integrate(&fxy2(), 0, y[i]^2, 40, y[i])
  }
  return(f)
}

: integrate(&f_inner2(), 0, 2)
32
```
Solution

real rowvector fxy2(real rowvector x, real rowvector y)
{
    return(6:*x:*y)
}

real rowvector f_inner2(real rowvector y)
{
    for(i=1; i<=cols(y);i++) {
        if (i==1) f=integrate(&fxy2(), 0, y[i]^2, 40, y[i])
        else f = f, integrate(&fxy2(), 0, y[i]^2, 40, y[i])
    }
    return(f)
}

: integrate(&f_inner2(), 0, 2)
32
Sample size re-estimation

Usually when designing a clinical trial we **pre-specify** the value of a treatment effect (and all the nuisance parameters) to find the sample size.

- We plan to do a single interim analysis to re-evaluate this sample size
- Going to apply the methods to a real trial example
Trial details

- Currently limited treatment options for Osteoarthritis (OA) of the knee. Not suitable or ineffective for many people. Surgery often only remaining option
- Methotrexate used effectively for Rheumatoid arthritis but not OA
- Promising results from pilot study (n=30) showed significant pain reduction for methotrexate in OA
- Study team proposed to test the drug’s performance in addition to standard care in a double blind, randomized, placebo controlled trial
The problem

• Initial grant application received positive feedback from funder
• Unfortunately it was rejected due to lack of evidence about the effect size likely to be seen in the RCT
Potential solution

Wanted to use a method that:

1. can be **fully specified** in advance of the trial;
2. can be implemented by an independent non-expert data monitoring committee;
3. is **not motivated** via a complex conditional error function; and
4. is motivated by clear decision framework linking interim effect size with future sample size via a **simple and familiar formula**
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4. is motivated by clear decision framework linking interim effect size with future sample size via a **simple and familiar** formula.
Notation

- Assume observations in experimental treatment group $X$ and standard therapy group $Y$ are normally distributed with means $\mu_X$ and $\mu_Y$ and have a common known variance of $\sigma^2$
- **Parameter** of interest is $\delta = \frac{\mu_X - \mu_Y}{\sigma}$. $H_0 : \delta \leq 0$
- Fixed design: $n$ patients per arm
- Choose $n = \frac{2}{\delta^2} (Z_\alpha + Z_\beta)^2$, where $Z_u = \Phi^{-1}(1 - u)$
- e.g. if $\delta = 0.35$, $\alpha = 0.025$ and $\beta = 0.2$ then $n = 128$ patients per arm

Estimation and inference for $\delta$

- $\bar{x} \sim N(\mu_X, \sigma^2/n)$, $\bar{y} \sim N(\mu_Y, \sigma^2/n)$ and $\hat{\delta} = \frac{\bar{x} - \bar{y}}{\sigma}$
- $z = \frac{\hat{\delta}}{\sqrt{2/n}} \sim N \left( \frac{\delta}{\sqrt{2/n}}, 1 \right)$
Notation

- Assume observations in experimental treatment group X and standard therapy group Y are normally distributed with means $\mu_x$ and $\mu_y$ and have a common **known variance** of $\sigma^2$.
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- $z = \frac{\hat{\delta}}{\sqrt{2/n}} \sim N\left(\frac{\delta}{\sqrt{2/n}}, 1\right)$.
• if $\delta << 0.35$ then substantially more than 128 people needed
• if $\delta >> 0.35$ then trial is a waste of resources
A general two stage strategy

- Suppose instead $n_1$ ($\ll n$) patients initially recruited giving:
  \[ \hat{\delta}_1 = \frac{\bar{x} - \bar{y}}{\sigma} \text{ and } z_1 = \frac{\hat{\delta}_1}{\sqrt{2/n_1}} \sim N\left(\frac{\hat{\delta}}{\sqrt{2/n_1}}, 1\right) \text{ at the interim analysis}. \]

Then if:

\[ \begin{cases} 
  z_1 > k & \text{: Stop the trial for efficacy} \\
  z_1 < h & \text{: Stop the trial for futility} \\
  h \leq z_1 \leq k & \text{: Recruit further } n_2 \text{ patients (} z_1 \uparrow \Rightarrow n_2 \downarrow) 
\end{cases} \]

Base inference at stage 2 on combined data via test statistic:

\[ z = \frac{\sqrt{n_1 z_1} + \sqrt{n_2(z_1)z_2}}{\sqrt{n_1 + n_2(z_1)}} \text{ Reject } H_0 \text{ if } z \geq C \]

How to choose design parameters $h, k, C$ and function $n_2(z_1)$?
A general two stage strategy

- Suppose instead $n_1$ ($\ll n$) patients initially recruited giving:

\[
\hat{\delta}_1 = \frac{\bar{x} - \bar{y}}{\sigma} \quad \text{and} \quad z_1 = \frac{\hat{\delta}_1}{\sqrt{2/n_1}} \sim N\left(\frac{\hat{\delta}}{\sqrt{2/n_1}}, 1\right)
\]

at the **interim analysis**. Then if:

\[
\begin{align*}
z_1 &> k : \text{Stop the trial for efficacy} \\
z_1 &< h : \text{Stop the trial for futility} \\
h &\leq z_1 \leq k : \text{Recruit further } n_2 \text{ patients (} z_1 \uparrow \Rightarrow n_2 \downarrow \text{)}
\end{align*}
\]

Base inference at stage 2 on **combined data** via test statistic:

\[
z = \frac{\sqrt{n_1} z_1 + \sqrt{n_2(z_1)} z_2}{\sqrt{n_1 + n_2(z_1)}} \quad \text{Reject } H_0 \text{ if } z \geq C
\]

How to choose design parameters $h$, $k$, $C$ and function $n_2(z_1)$?
Chosing h,k,C via the Li et al. method

- Choose an overall type I error $\alpha$ and conditional power $1 - \beta_1$
- Choose $h$ and $k$ almost freely (e.g based on p-value for $z_1$)
  - There are restrictions based on the error probabilities
- Find $C$ such that:
  1. $P(z_1 > k|\delta = 0) + P(z > C|\delta = 0; h < z_1 < k) = \alpha$
  2. $P(z > C|\delta = \hat{\delta}_1, h < z_1 < k) \geq 1 - \beta_1$

Given $n_2(z_1) = \left( \frac{(C + Z_{\beta_1})^2}{z_1^2} - 1 \right) n_1$, for $z_1 \in (h, k)$

- A very simple method
- No complex conditional error function (Proschan and Hunsberger, 1995)
- Critical value $C$ independent of $z_1$
  - Whole design and analysis can be specified in advance
Finding C

From Li et al. (2002) they state that one can use numerical integration to solve

\[ 1 - \Phi(h) - \alpha = \int_{h}^{k} \Phi \left( \frac{C(C + Z_{\beta_1}) - z_1^2}{\sqrt{(C + Z_{\beta_1})^2 - z_1^2}} \right) \phi(z_1) dz_1 \]

this is solved for \( c \) (the other design parameters are selected previously)

Need to use optimize() and integrate() together!!
real rowvector findC(real rowvector x, real rowvector arg)
{
    c = arg[1]
    Zb = arg[2]
    return(normal((c+(c+Zb)-x.^2):/sqrt((c+Zb)^2-x.^2)):normalden(x))
}

void evalC(todo, c, h, k, alpha, Zb, y, g, H)
{
    y=(integrate(&findC(),h,k,60,(c, Zb))-(1-normal(h)-alpha))^2
}

void calculateC(h, k, alpha, power)
{
    Zb = invnormal(power)
    C = optimize_init()
    optimize_init_which(C, "min")
    optimize_init_evaluator(C, &evalC())
    optimize_init_tracelevel(C, "none")
    optimize_init_params(C, 1)
    optimize_init_argument(C,1,h)
    optimize_init_argument(C,2,k)
    optimize_init_argument(C,3,alpha)
    optimize_init_argument(C,4,Zb)
    c = optimize(C)
}
Programming up finding C

```plaintext
real rowvector findC(real rowvector x, real rowvector arg)
{
    c=arg[1]
    Zb = arg[2]
    return( normal((c:*c:Zb:n-x:2):/sqrt((c:Zb:2:-x:2)):normalden(x) )
}
void evalC(todo, c, h, k, alpha, Zb, y, g, H)
{
    y=(integrate(&findC(),h,k,60,(c, Zb))-(1-normal(h)-alpha))^2
}
void calculateC(h, k, alpha, power)
{
    Zb=invnormal(power)
    C = optimize_init()
    optimize_init_which(C, "min")
    optimize_init_evaluator(C, &evalC())
    optimize_init_tracelevel(C, "none")
    optimize_init_params(C, 1)
    optimize_init_argument(C,1,h)
    optimize_init_argument(C,2,k)
    optimize_init_argument(C,3,alpha)
    optimize_init_argument(C,4,Zb)
    c = optimize(C)
}
```
Stata code for Sample size re-estimation

```
. ssr
Sample Size Re-estimation
------------------------------------
The following are set in the first stage
The sample size per arm is 50
The futility bound is 1
The efficacy bound is 2.76
The conditional power is .8
The unconditional power is .8

The Li et al. critical value is 1.923

+------------------------------------------------------------------+
| NOTE |
| A fixed sample size requires 129 people |
| for a treatment effect of .35, |
| unconditional power .8 and |
| one-sided significance of .025 |
+------------------------------------------------------------------+
```
ssr, graph

129 is the fixed design sample size
Conclusions

- **integrate** is a flexible function
  - Still need to get a better Gauss-Hermite solution
- **ssr**, the Stata command, is available to design sample size re-estimation
  - there are several methods that are available in a future publication Bowden and Mander