Numerical Integration with an application to Sample size re-estimation

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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

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

where w_j are weights and x_j are the abscissas.

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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.

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How to find the weights/abscissas

The roots of the Legendre polynomial defined by

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\begin{aligned}
P_0(x) &= 1 \\
P_1(x) &= x \\
(n+1)P_{n+1}(x) &= (2n+1)xP_n(x) - nP_{n-1}(x)
\end{aligned}
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Similarity Matrix corresponding to Legendre polynomial

$$\begin{pmatrix} 0 & \frac{1}{\sqrt{4*1^2-1}} & & & \\ \frac{1}{\sqrt{4*1^2-1}} & 0 & \frac{2}{\sqrt{4*2^2-1}} & & \\ & \frac{2}{\sqrt{4*2^2-1}} & \ddots & \ddots & \\ & & \ddots & & \\ & & & 0 & \frac{n-1}{\sqrt{4*(n-1)^2-1}} \\ & & & \frac{n-1}{\sqrt{4*(n-1)^2-1}} & 0 \end{pmatrix}$$

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

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Basic syntax

To calculate the following expression

$$\int_a^b f(x)\ \mathrm{dx}$$

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)
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- $-\infty$ is specified by setting $a = .$
- similarly, if $b = .$ then the upper limit is ∞

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Simple example - Stata

$$\int_0^3 x^2 \mathrm{d}x \tag{1}$$

Using the Stata command

```
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 ~/ado/personal/ (make sure this is writeable)

The integral = 9
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Could have done

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integrate, f(x^2) l(0) u(3) vectorise
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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.

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

Then to integrate this function type with Mata

```
: integrate(&f(), 0, 3)
  9
```

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**

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Double Integration

$$\int_0^1 \int_0^1 x + y \ \mathrm{dx}\ \mathrm{dy}$$

Want to just write

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integrate( integrate(&f(),0,1) ,0,1)
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- However `integrate()` does not return a rowvector so this syntax would **fail**

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Solution

First define

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

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)
}

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

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  1
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Further Double Integration

$$\int_0^2 \int_0^{y^2} 6xy \text{ dx dy}$$

This is also a simple extension to the previous code

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

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```

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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Notation

- Assume observations in experimental treatment group X and standard therapy group Y are normally distributed with means μ_x and μ_y and have a common **known variance** of σ^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 δ

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

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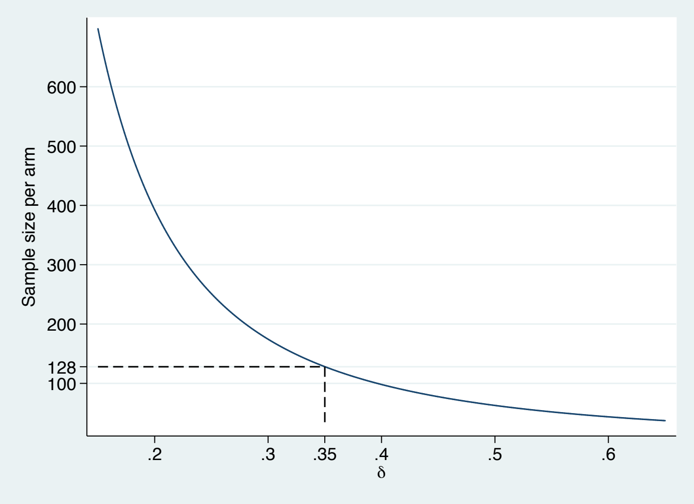

- if $\delta << 0.35$ then substantially more than 128 people needed
- if $\delta >> 0.35$ then trial is a waste of resources

A general two stage strategy

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

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

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

$$z = \frac{\sqrt{n_1}z_1 + \sqrt{n_2(z_1)}z_2}{\sqrt{n_1 + n_2(z_1)}} \text{ Reject } H_0 \text{ if } z \ge C$$

How to choose design parameters h, k, C and function $n_2(z_1)$?

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Chosing h,k,C via the Li et al. method

- Choose an overall type I error α 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

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

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

Need to use optimize() and integrate() together!!

Programming up finding C

```
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)
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 optimize_init_argument(C,4,Zb)
 c = optimize(C)
}
```

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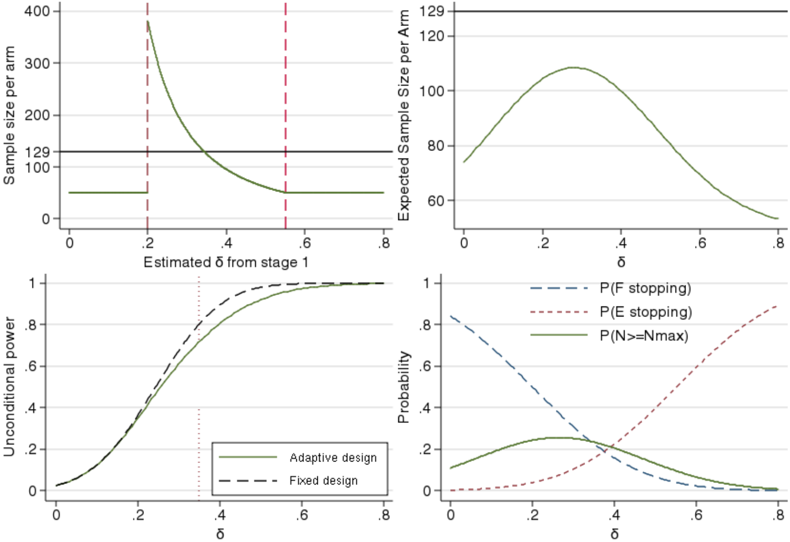
Stata code for Sample size re-estimation

```
. 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