Inference in Covariate-Adaptive allocation

Elsa Valdés Márquez & Nick Fieller

MPS Research Unit, University of Reading &

Department of Probability and Statistic, University of Sheffield

EFSPI Adaptive Randomisation Meeting

Brussels, 7 December 2006

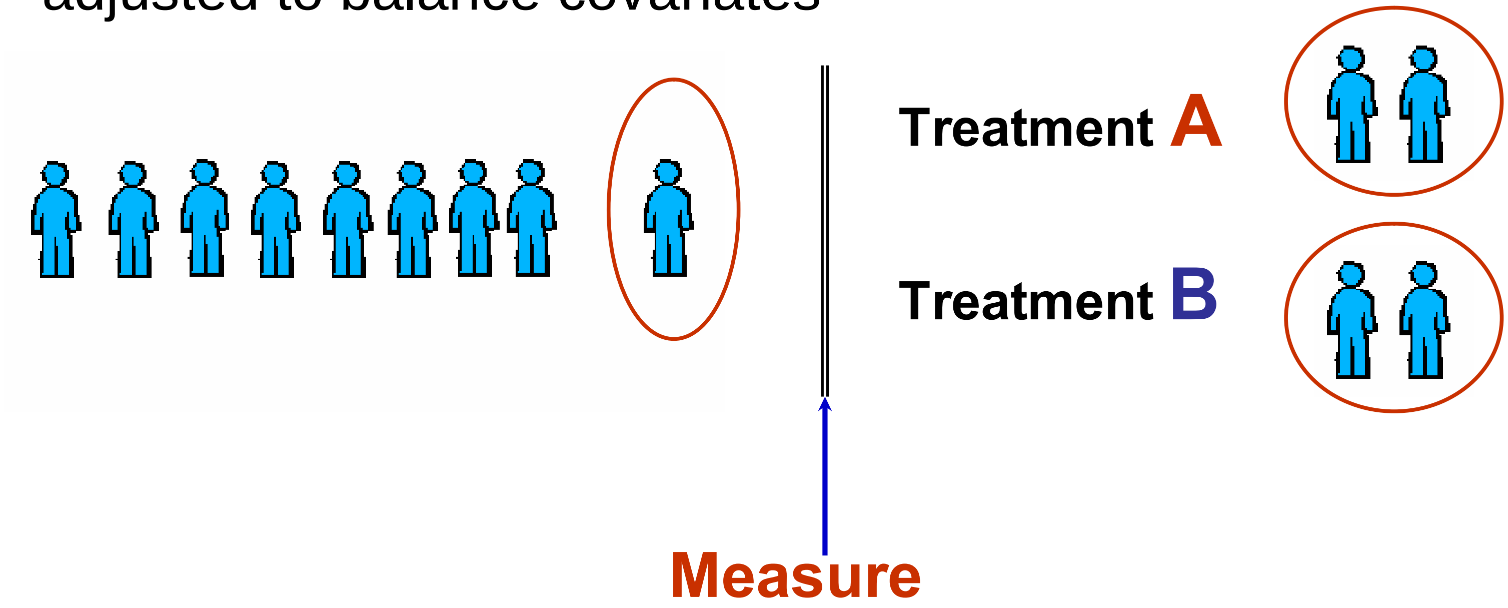
OUTLINE

- Introduction
- Performance Comparison
  - Efficiency
- Inference
  - Randomisation tests
    confidence intervals etc
- Summary

Covariate-Adaptive Methods

General Rule:

- Imbalance measure
  (prognostic factors of *previous* patients **&** *new* patient)
- Treatment allocation probability
  adjusted to balance covariates



Some methods

Minimization aims to reduce marginal imbalance over each factor
either deterministically (*Taves,1974*)
or with bias in random element (*Pocock & Simon, 1975*)

Methods based on D-Optimum design:

- ***D_S-Optimum design***
  minimizes variance of treatment effect by deterministic allocation
  (Begg & Iglewicz, 1980)

- ***D_A-Optimum biased coin design***
  combines DA-Optimality criterion & biased coin design allocation
  (Atkinson, 1982)

Performance Comparison (for two treatments)

- **Loss of Efficiency (Atkinson, 1999)**

$$E(Y) = \mathbf{z}\alpha + \mathbf{X}\beta$$

Treatment difference (α)

A constant term and k prognostic factors ($\mathbf{X}$)

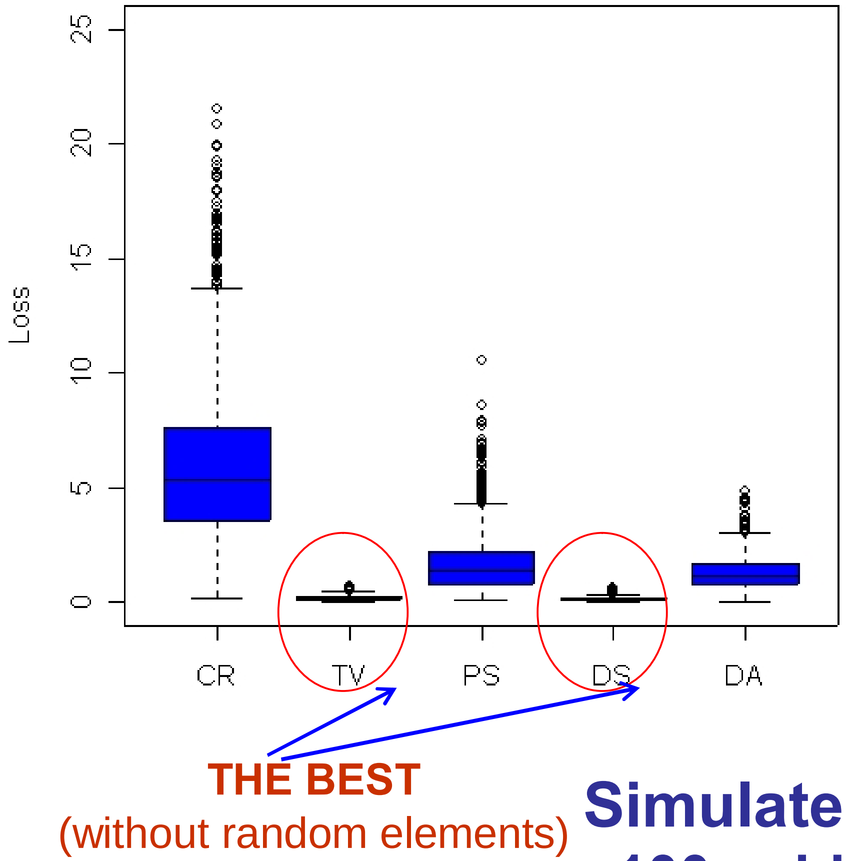
$$Var(\hat{\alpha}) = \frac{\sigma^2}{\mathbf{z}^T\mathbf{z} - \mathbf{z}^T\mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{z}}$$

Loss → $L_n = \mathbf{z}^T\mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{z}$

(for **n** patients and **k** factors;
X a n×k design matrix)

Performance Comparison

Loss of efficiency of various methods



CR: Complete Randomization

TV: Minimization *(Taves,1974)*

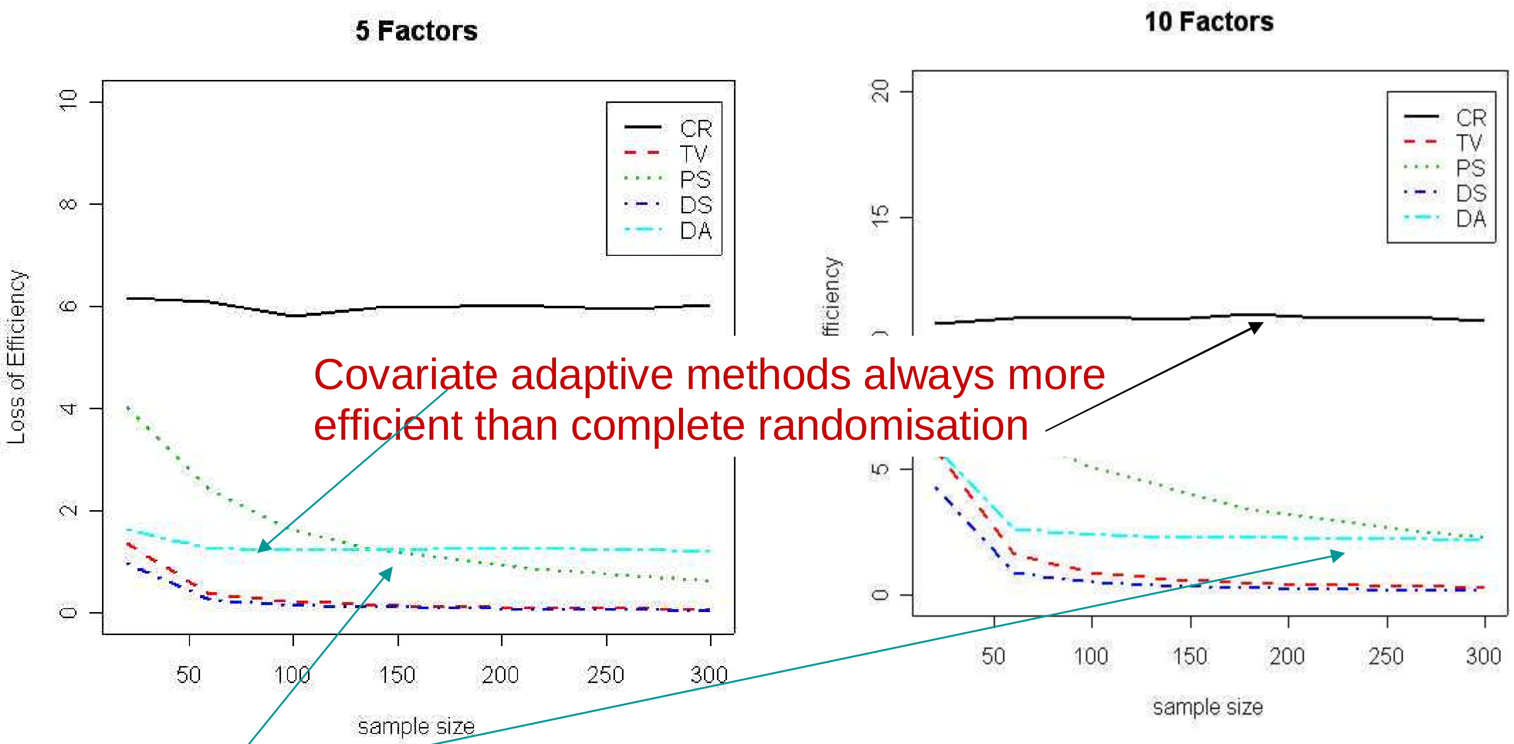
PS: Minimization
(Pocock & Simon, 1975)

Ds: Ds-Optimum Design
(Begg&Iglewicz, 1980)

DA: DA-Optimum
Biased Coin Design
(Atkinson,1982)

Simulated data:-
100 subjects, 5 prognostic factors

Different factors and samples



Covariate adaptive methods always more efficient than complete randomisation

method with random element (PS) only efficient for larger sample sizes

1,000 group of patients

Inference

"Randomization models the outcome variable of interest as fixed & the treatment assignment (designs points) as random;

in a population model we traditionally treat the variable of interest as random at fixed values of the design points"

Rosenberger and Lanchin (2002)

Randomization model

The distribution of the test statistic depends on the randomization procedure

Population model

The use of complete randomization or covariate-adaptive allocation methods does not influence the inferential procedure

Randomization Model

Permutation tests

The reallocation of the patients to treatments should be in a manner consistent with original assignment

Two situations:

- *(Exact A)* Patients arrive by chance in any order and they could equally well arrive in any other
- *(Exact B)* The arrival order of the patients is important Fixed order

Past work on permutation tests:
Metha, et.al. (1988), Smythe & Wie (1983),
Hollander & Peña (1988), France (1998)

+ Ebutt et. al. (1997) considers both fixed & random orders of subjects

Randomization Model

- *(**Exact A**)* Patients arrive by chance in any order and they could equally well arrive in any other order

Randomisation distribution obtained by permuting the order of subjects & reapplying minimisation algorithm

- *(**Exact B**)* The arrival order of the patients is important

Condition on order and then randomisation distribution obtained only from random elements in allocation
(including resolution of ties in deterministic methods such as Taves)

Toy Example

Objective: Test effect of Captopril on kidney function
in insulin-dependent diabetic patients with nephropathy

Number of patients: 16

Prognostic Factors

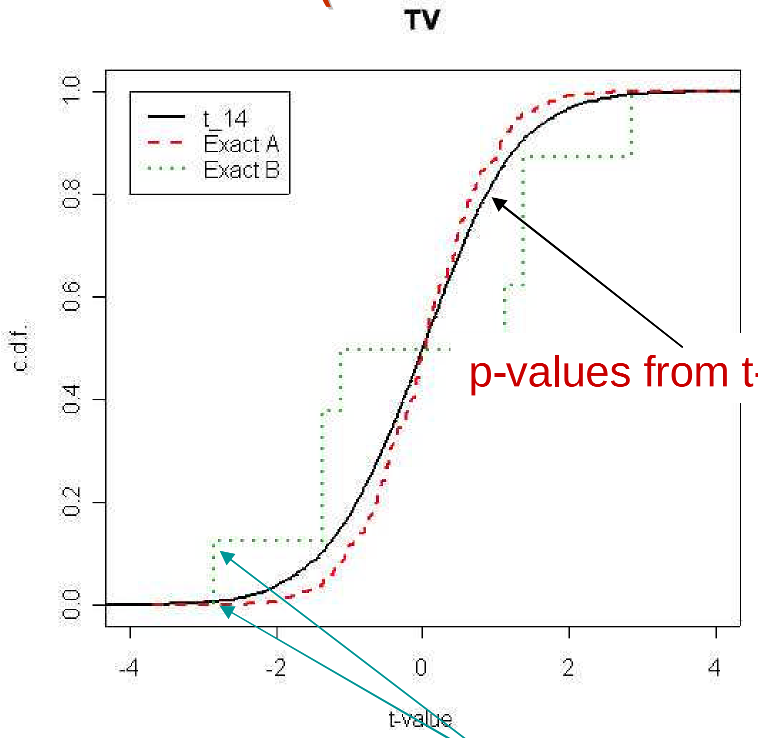
Age, Duration of diabetes,Insulin dose,

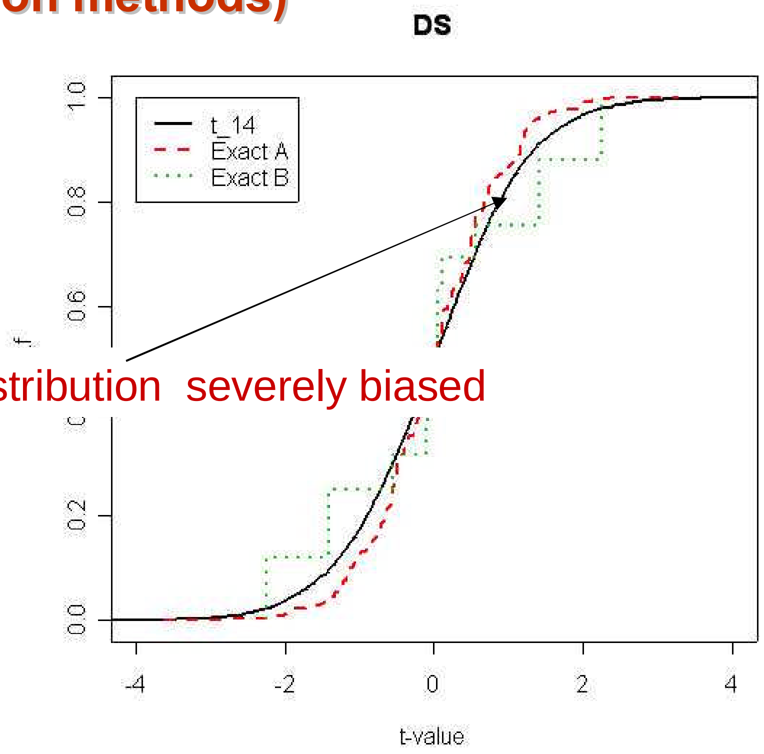
Systolic blood pressure, Diastolic blood pressure

Response: Glomerular filtration rate (ml/min/1.73M^2)

16 subjects selected from larger data set –
unrealistically small number of subjects but illustrates main features

Toy example : Randomisation Distribution (Deterministic allocation methods)





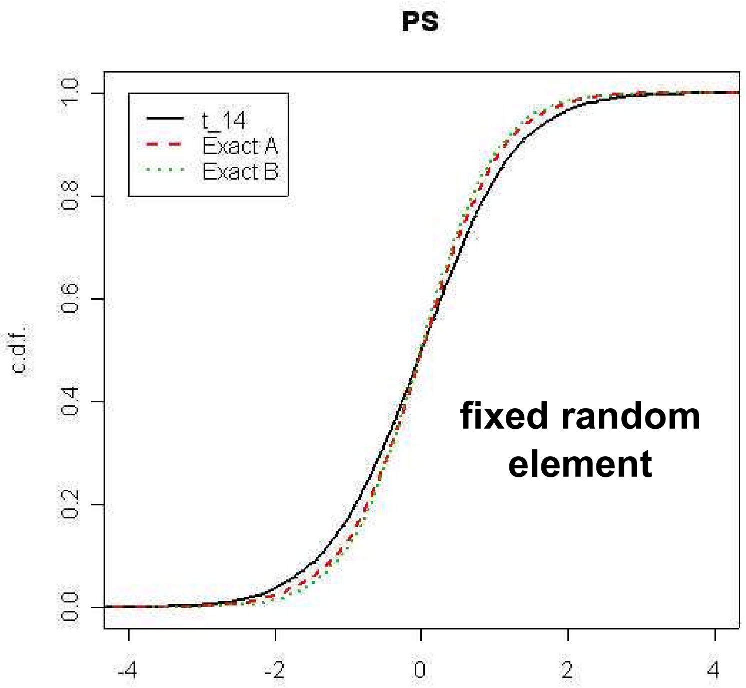
p-values from t-distribution severely biased

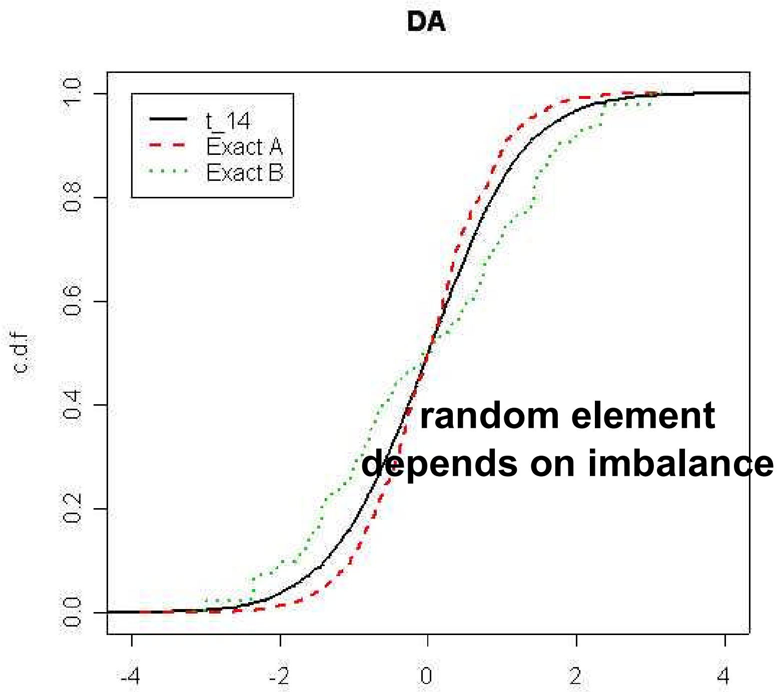
only discrete choice of achievable p-values with assumption B

more p-values available with Optimal Design based methods

5,000 times

Toy example : Randomisation Distribution
(allocation methods with random elements)





t-distribution now a good approx to randomisation distribution

t-approximation more biased

5,000 times

Toy example (16 subjects): p-values

Method:-	TV	PS	DS	DA
Classical	0.0147	0.0734	0.0176	0.0681
Exact A	0.0140	0.0758	0.0146	0.0632
Exact B	**0.0642**	0.0392	**0.1240**	0.0740
Value of test statistic	-2.4248	-1.5362	-2.3239	-1.5806

p-values with fixed order of subjects (assumption B)
very different from those given by classical t-distribution

Example 2 Cirrhosis : p-values
(with adjustment of test statistic for covariates)

Distribution	TV	PS	DS	DA
Classical	0.0024	0.0225	0.0244	0.0768
Exact A	0.0018	0.0116	0.0138	0.0368
Exact B	**0.0592**	0.0124	**0.0546**	0.0454
Value of test statistic	2.3669	2.3338	1.8133	1.1518

5 prognostic factors and ***50*** *patients*

Similar features with larger data set &
test statistic adjusted for covariate differences

Confidence intervals

- Guaranteed method for constructing randomisation distribution based confidence intervals as inverse of significance tests is very time consuming
  – can be obtained only by ‘trial & error’
  - CI is set of points ***not*** rejected by a test
- usual standard error measures variability under ***complete randomisation***
  - (e.g. note that s^2 is unbiased for population variance only under CR)
- Need an approximate method based on ‘pseudo standard errors’ (or ***effective*** s.e.)
- pseudo (or effective) s.e. measures variability under restricted randomisation used in the permutation tests
  - then use this with t-distribution for approx ‘pseudo CIs’

Pseudo-Confidence Intervals

$$\text{Pseudo} - \text{SE} = \frac{\left|\bar{X}_1 - \bar{X}_2\right|}{t_{n-2}^{-1}(\text{exact p - value})}$$

t–distribution

Randomization test

i.e. choose the pseudo standard error in a classical t-test to give the same correct p-value as that given by the randomisation test

so we can use this with a t-value for obtaining a pseudo CI

$$\bar{X}_1 - \bar{X}_2 \pm t_{n-2,\alpha/2} \times \left(\text{Pseudo} - \text{SE}\right)$$

Some related work:

Chan and Zhang (1999), Agresti & Min (2001) and Miettinen & Nurminen (1985)

Example: 95% Confidence Intervals

Method	$\bar{X}_1 - \bar{X}_2$	Classical	Pseudo A	Pseudo B
TV	-21.701	[-40.894,-2.506]	[-40.690,-2.710]	[-50.501,7.101]
PS	-13.625	[-32.648,5.398]	[-32.893,5.642]	[-29.016,1.765]
DS	-20.818	[-40.031,-1.665]	[-39.238,-2.398]	[-55.551,13.158]
AT	-13.928	[-32.831,4.972]	[-32.310,4.452]	[-33.439,5.581]

Diabetes example

Summary

- Covariate-adaptive allocation methods are more efficient than Complete Randomization
- Use of randomization distribution is alternative for Covariate-Adaptive allocation methods
- Confidence intervals with a pseudo standard error may be an option for Covariate-Adaptive allocation methods