Cost constrained optimal designs for regression models with random parameters

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Model

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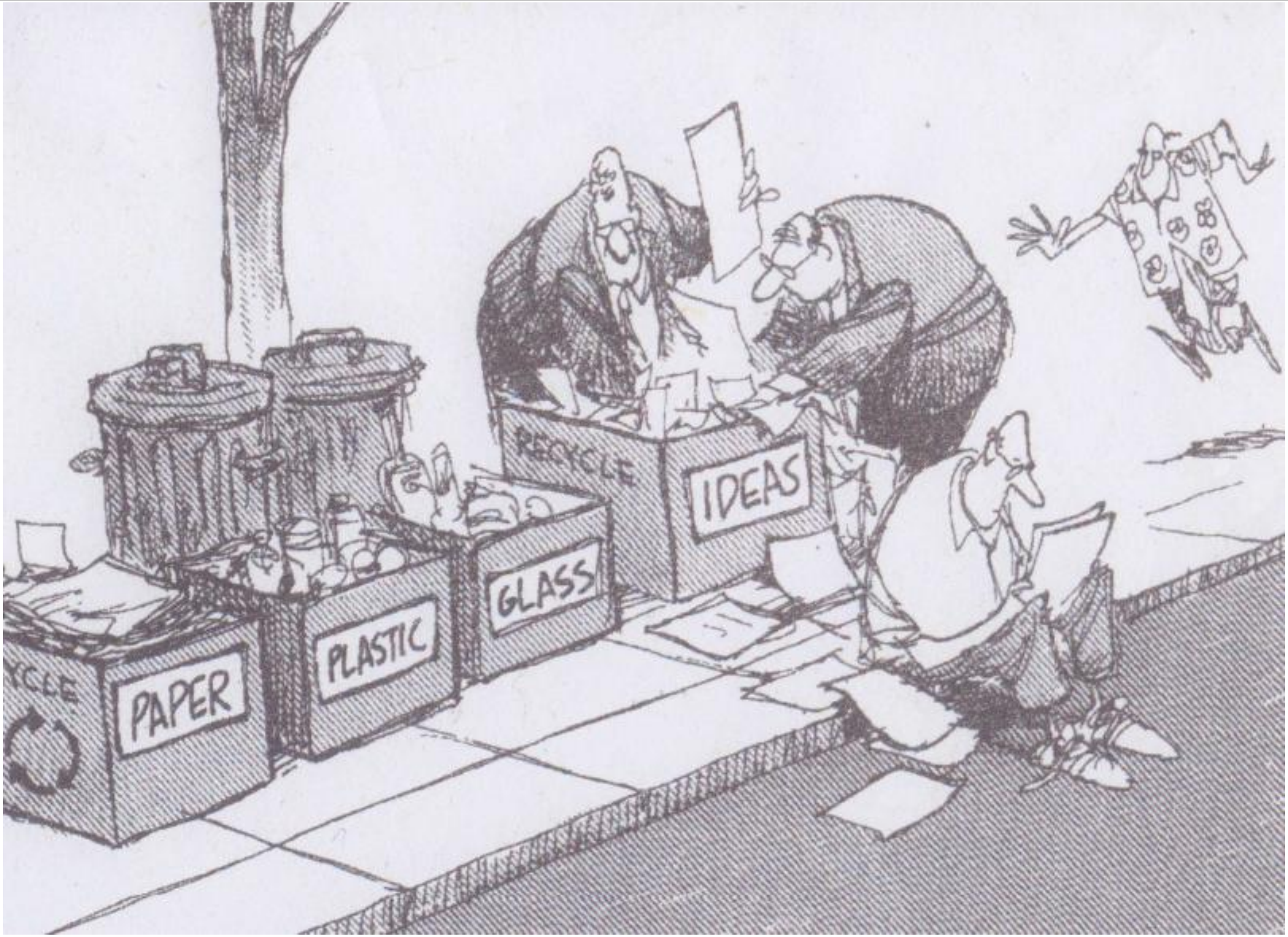
$$\mathbf{y}_{ij} = \mathbf{F}^T(\mathbf{x}_{ij})\gamma_i + \varepsilon_{ij}$$

- Number of centers n
- Treatment effect in the i-th center is described by γ_i that is random with mean γ^0 and var-cov matrix $\boldsymbol{\Omega}$
- Observational errors (between subject variability) ε_{ij} have zero means and variance σ^2, are uncorrelated between each other and with γ_i
- At $\mathbf{x}_{ij}$ we have r_{ij} subjects and $r_i = \sum_{j=1}^{k_i} r_{ij}$
- We are interested in estimation individual and global parameters

Fedorov V. and Jones B. The design of multicenter trials, *Statistical Methods in Medical Research*, (2005). **14**, 205-248

Our approach



Linear estimators

- Total sum of squared deviations

$$
\begin{aligned}
SS &= \sum_{i=1}^{n}\sum_{j=1}^{r_i}\left[\mathbf{y}_{ij}-\mathbf{F}^T(\mathbf{x}_{ij})\gamma_i\right]^T\left[\mathbf{y}_{ij}-\mathbf{F}^T(\mathbf{x}_{ij})\gamma_i\right] \\
&= \sum_{i=1}^{n}\left[\mathbf{S}_i+(\bar{\gamma}_i-\gamma_i)^T(\underline{\mathbf{M}}_i+\mathbf{\Omega}^{-1})(\bar{\gamma}_i-\gamma_i)\right] \\
&+ \sum_{i=1}^{n}(\widehat{\gamma}_i-\gamma^0)^T(\underline{\mathbf{M}}_i^{-1}+\mathbf{\Omega})^{-1}(\widehat{\gamma}_i-\gamma^0).
\end{aligned}
$$

- Notations

$$
\underline{\mathbf{M}}_i = \sigma^{-2}r_i\mathrm{M}(\xi_i)=\sigma^{-2}r_i\sum_{j=1}^{r_i}p_{ij}\,\mathrm{F}(\mathrm{x}_{ij})\mathrm{F}^T(\mathrm{x}_{ij})
$$

$$
\mathbf{S}_i = \sum_{j=1}^{r_i}\left[\mathbf{y}_{ij}-\mathbf{F}^T(\mathbf{x}_{ij})\widehat{\gamma}_i\right]\ \left[\mathbf{y}_{ij}-\mathbf{F}^T(x_{ij})\widehat{\gamma}_i\right]^T
$$

$$
\widehat{\gamma}_i = \underline{\mathbf{M}}_i^{-1}\underline{\mathbf{Y}}_i,\quad \bar{\gamma}_i = \left(\underline{\mathbf{M}}_i+\mathbf{\Omega}^{-1}\right)^{-1}\left(\underline{\mathbf{M}}_i\widehat{\gamma}_i+\mathbf{\Omega}^{-1}\gamma^0\right)
$$

$$
\underline{\mathbf{Y}}_i = \sigma^{-2}r_i\mathbf{Y}_i=\sigma^{-2}r_i\sum_{j=1}^{r_i}p_{ij}\,\mathrm{F}(\mathrm{x}_{ij})\mathrm{y}_{ij},\quad \xi_i = \{\mathrm{x}_{ij},\,p_{ij}\},\ \ p_{ij}=r_{ij}/r_i
$$

C.R. Rao. The theory of least squares when the parameters are stochastic and its application to the analysis of growth curves. Biometrika, 52(3/4):447–458, 1965

E. Spjotvoll. Random coefficients regression models. A Review. Statistics,8:69–93, 1977.

Optimal design for individual parameters

$$\mathbf{D}(\widehat{\gamma}_i) = \mathrm{E}_\varepsilon \left[(\widehat{\gamma}_i - \gamma_i) \, (\widehat{\gamma}_i - \gamma_i)^T \, | \gamma_i \right] = \underline{\mathbf{M}}_i$$

$$\mathbf{D}(\bar{\gamma}_i) = \mathrm{E}_{\boldsymbol{\gamma}} \mathrm{E}_\varepsilon \left[(\bar{\gamma}_i - \gamma_i) \, (\bar{\gamma}_i - \gamma_i)^T \right] \;=\; \left(\underline{\mathbf{M}}_i + \boldsymbol{\Omega}^{-1} \right)^{-1}$$

Two optimization problems:

$$\xi^* = \arg\min_{\xi} \Psi \left[\mathrm{M}(\xi) \right], \text{ where } \mathrm{M}(\xi) = \int_{\mathfrak{X}} \mathrm{F}(\mathrm{x}) \mathrm{F}^T(\mathrm{x}) \xi(d\mathrm{x})$$

and

$$\xi^* = \arg\min_{\xi} \Psi \left[\mathrm{M}_{tot}(\xi) \right], \text{ where } \mathrm{M}_{tot}(\xi) = \mathrm{M}(\xi) + r_i^{-1} \Omega^{-1}$$

Nothing special but in the second case optimal design depends on number of subjects and the population var-cov matrix.

Population mean (treatment effect)

- BLUE:

$$\widehat{\gamma}^0 = \left[\sum_{i=1}^{n} (\underline{\mathbf{M}}_i^{-1} + \mathbf{\Omega})^{-1}\right]^{-1} \sum_{i=1}^{n} (\underline{\mathbf{M}}_i^{-1} + \mathbf{\Omega})^{-1} \widehat{\gamma}_i = \sum_{i=1}^{n} W_i \widehat{\gamma}_i$$

$$W_i \sim (\underline{\mathbf{M}}_i^{-1} + \mathbf{\Omega})^{-1}, \ \sum_i W_i = 1$$

$$\mathrm{Var}(\widehat{\gamma}^0) = \left[\sum_{i=1}^{n} (\underline{\mathbf{M}}_i^{-1} + \mathbf{\Omega})^{-1}\right]^{-1}$$

→

$$\mathrm{Var}(\widehat{\gamma}^0) = \left[\sum_{i=1}^{n} N_i (\underline{\mathbf{M}}_i^{-1} + \mathbf{\Omega})^{-1}\right]^{-1}$$

$$M_{pop}(\Xi) = \left[\sum_{i=1}^{n} \pi_i (r_i^{-1} \mathbf{M}^{-1}(\xi_i) + \mathbf{\Omega})^{-1}\right]^{-1}$$

$$N = \sum_{i=1}^{n} N_i, \quad \pi_i = N_i / N$$

$$\Xi^* = \arg\min_{\Xi} \Psi \left[\mathbf{M}_{pop}(\Xi)\right]$$

F. Mentr´e, A. Mallet, and D. Baccar. Optimal design in random-effects regression models. *Biometrika*, 84(2):429–442, 1997

The simplest case

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- Let $\xi_i \equiv \xi,\ r_i \equiv r$ and $\underline{\mathbf{M}}_i \equiv \underline{\mathbf{M}}$
  then

$$\mathrm{Var}(\widehat{\gamma}^0) = \frac{1}{N} \left(\underline{\mathbf{M}}^{-1} + \mathbf{\Omega}\right)$$

  and

$$\xi^* = \arg\min_{\xi} \ \Psi\left[\left(r^{-1}\mathbf{M}^{-1}(\xi) + \mathbf{\Omega}\right)^{-1}\right]$$

- If N and r are fixed then:

$$\xi^* = \arg\min_{\xi} \ \mathrm{tr}\left\{\frac{\mathbf{A}}{Nr}\left[\mathbf{M}^{-1}(\xi) + r\mathbf{\Omega}\right]\right\} = \arg\min_{\xi} \ \mathrm{tr}[\mathbf{A}\mathbf{M}^{-1}(\xi)]$$

Fedorov V and Leonov S (2013), CRC

Working with cost

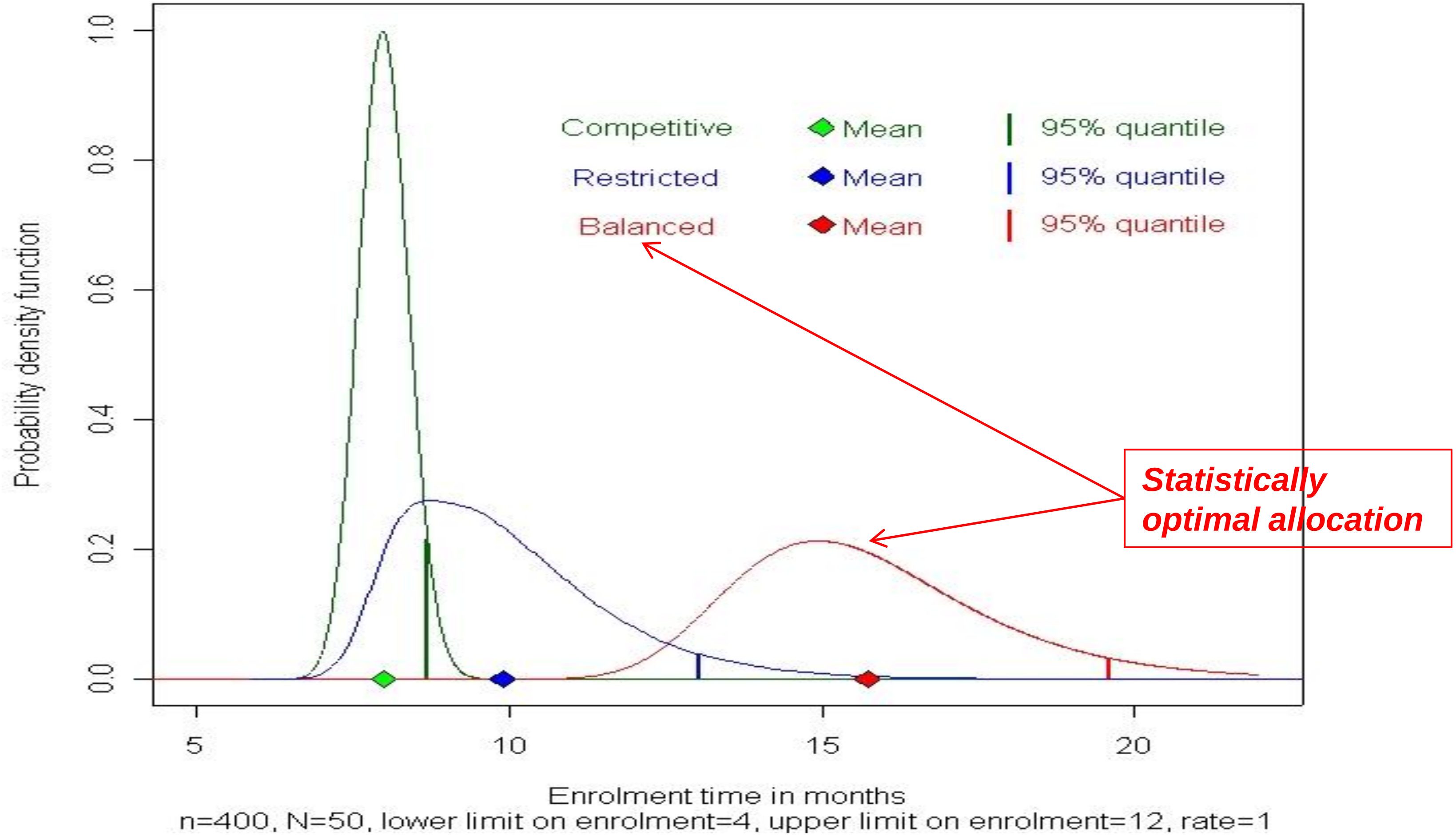
Cost function: $Q = Nr + Nq$ → $N = Q/(r+q)$

$$\Psi_{Nr} = \mathrm{tr}\left\{\mathbf{A}\left[\frac{\mathbf{M}^{-1}(\xi)}{Nr} + \frac{\mathbf{\Omega}}{N}\right]\right\} = \left\{\frac{\mathrm{tr}[\mathbf{A}\mathbf{M}^{-1}(\xi)]}{r} + \mathrm{tr}(\mathbf{A}\mathbf{\Omega})\right\}\frac{r+q}{Q}$$

$$r^* = \sqrt{q\,\frac{\mathrm{tr}[\mathbf{A}\mathbf{M}^{-1}(\xi)]}{\mathrm{tr}(\mathbf{A}\mathbf{\Omega})}}$$

$$\Psi_{Nr} = Q^{-1}\left\{\sqrt{\mathrm{tr}[\mathbf{A}\mathbf{M}^{-1}(\xi)]} + q\sqrt{\mathrm{tr}(\mathbf{A}\mathbf{\Omega})}\right\}^2$$

Random enrollment: waiting time



For $1 billion drug one lost day costs ~$2.7M. What is the cost to enroll and to treat extra 100 subjects?

Random enrollment: variance inflation

Variance of the estimator of the ECRT under increasingly more general assumptions

Case	Variance
Fixed centres and treatments, deterministic balanced enrollment	$\frac{4\sigma^2}{n}$
Random treatment effects, deterministic balanced enrollment	$\frac{4\sigma^2}{n} + \frac{s^2}{N}$
Random treatment effects, random enrollment equal enrollment rates	$\frac{4\sigma^2}{n} + \frac{s^2}{N}\left[\frac{2N+n-2}{n}\right]$
Random treatment effects, random enrollment, varying enrollment rates	$\frac{4\sigma^2}{n} + \frac{s^2}{N}\left[\frac{2N+n-2}{n} + \frac{n-2}{n}\omega^2\right]$

$$\mathrm{Var}(\hat{\delta}) = \left(\frac{\delta^*}{z_{1-\alpha} + z_{1-\beta}}\right)^2$$

Optimization problem that address the lost revenues

Optimization problem: find

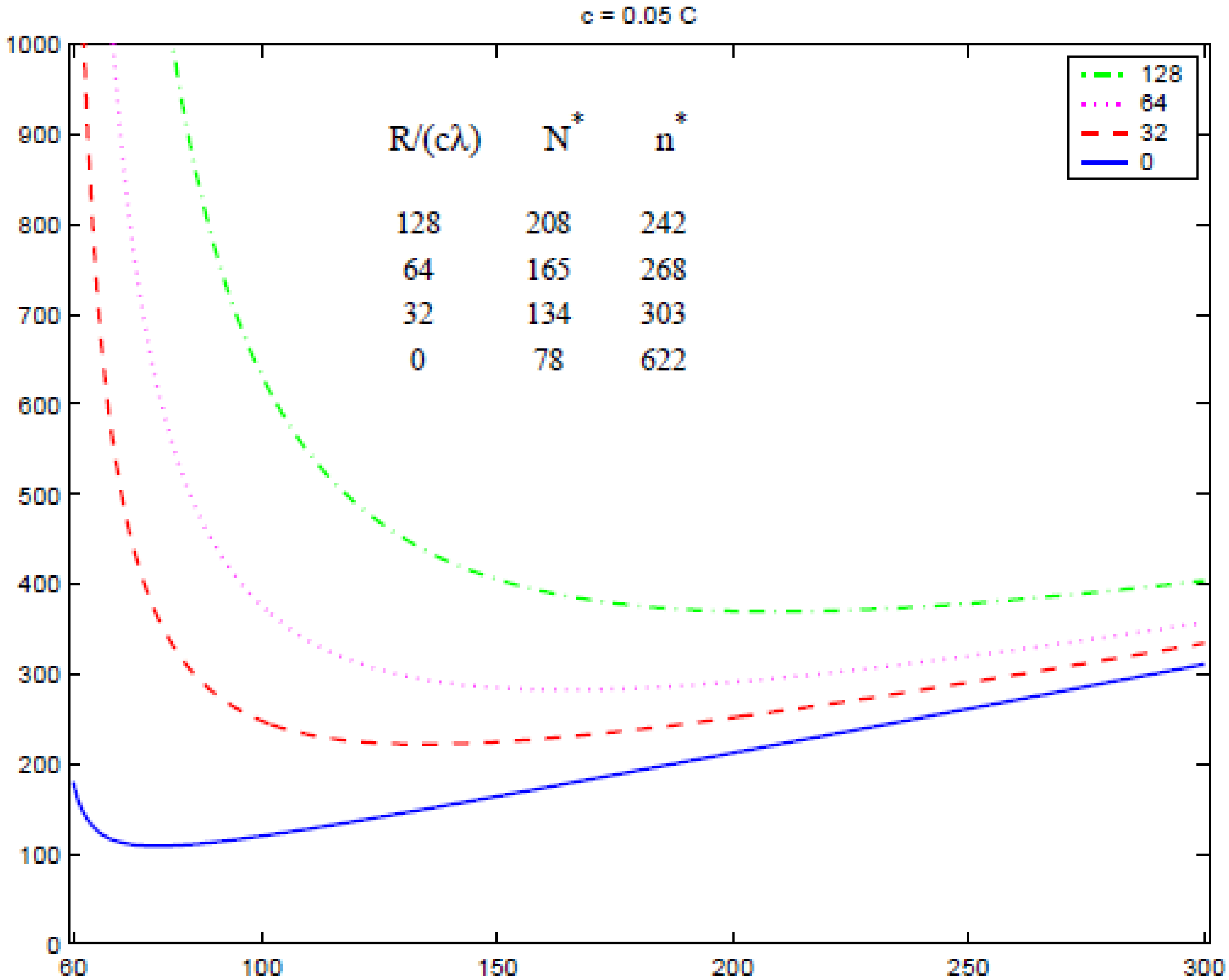
$$\{n^*, N^*\} = \arg\min_{n,N}\{CN + cn + d\frac{n}{N}\}$$

given that

$$\frac{4\sigma^2 + 2s^2}{n} + \frac{s^2}{N}\left(1 + \omega^2\right) \leq v^2$$

where $d = R/\bar{\lambda}$ and v^2 = targeted variance of estimated ECRT.

Example of risk minimization



Additional sources of potential variance inflation for nonlinear models

- Linearization:

$$F(\mathbf{x}_{ij},\boldsymbol{\gamma}_i) = \frac{\partial \eta(\mathbf{x}_{ij},\boldsymbol{\gamma})}{\partial \boldsymbol{\gamma}}|_{\boldsymbol{\gamma}=\boldsymbol{\gamma}_i} \;\Rightarrow\; F(\mathbf{x}_{ij})$$

$$\mathbf{M}(\xi_i) = \sum_{j=1}^{r_i} p_{ij}\,\mathbf{F}(\mathbf{x}_{ij})\mathbf{F}^T(\mathbf{x}_{ij}) \;\Rightarrow\; \mathbf{M}(\xi_i,\boldsymbol{\gamma}_i) = \sum_{j=1}^{r_i} p_{ij}\,\mathbf{F}(\mathbf{x}_{ij},\boldsymbol{\gamma}_i)\mathbf{F}^T(\mathbf{x}_{ij},\boldsymbol{\gamma}_i)$$

$$\mathbf{M}_{pop}(\Xi) = \sum_{i=1}^{n} \pi_i (r_i^{-1}\mathbf{M}^{-1}(\xi_i) + \boldsymbol{\Omega})^{-1} \;\Rightarrow\; \mathbf{M}_{pop}(\Xi,\boldsymbol{\gamma}^0,\boldsymbol{\Omega}) = \sum_{i=1}^{n} \pi_i N_i^{-1}\left[\sum_{i'=1}^{N_i}(r_i^{-1}\mathbf{M}^{-1}(\xi_i,\boldsymbol{\gamma}_{i'}) + \boldsymbol{\Omega})^{-1}\right]$$

Asymptotic results

- For large N

$$\mathbf{M}_{pop}(\Xi, \gamma^0, \mathbf{\Omega}) \Rrightarrow \sum_{i=1}^{n} \pi_i \mathrm{E}\left[(r_i^{-1}\mathbf{M}^{-1}(\xi_i, \gamma) + \mathbf{\Omega})^{-1}\right]$$

- When $\xi_i \equiv \xi,\, r_i \equiv r$ the previous optimization problem

$$\xi^* = \arg\min_{\xi} \; \Psi\left[(r^{-1}\mathbf{M}^{-1}(\xi) + \mathbf{\Omega})^{-1}\right]$$

have to be replaced with

$$\xi^* = \arg\min_{\xi} \; \Psi\left[\mathrm{E}\left[(r^{-1}\mathbf{M}^{-1}(\xi, \gamma) + \mathbf{\Omega})^{-1}\right]\right]$$

not with (!!!)

$$\xi_B^* = \arg\min_{\xi} \; \mathrm{E}\{\Psi[(r^{-1}\mathbf{M}^{-1}(\xi, \gamma) + \mathbf{\Omega})^{-1}]\}$$

Summary

- Optimal designs (allocations) may depend on N, r and cost function
- Often it is easy (cheaper) to enrolled more than to maintain the exact balance.
- Operational randomness may cause the variance inflation
- In the nonlinear case individual matrices are random
- It is promising to work with quantiles instead of means and talk about the probability of technical success