Recruitment to Phase III Clinical Trials

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Introduction

Definition

A clinical trial is a planned experiment on human beings which is designed to evaluate the effectiveness of one, or more, forms of treatment. [Altman, 1991]

Current Statistics

- Out of 114 trials studied, less than 1/3 of trials achieved the recruitment target in the time period and 1/3 of trials had to have extensions. [Campbell et al., 2007]
- Out of 1017 trials studied, 24.9% of trials were discontinued, 39.9% of these were discontinued due to poor recruitment. [Kasenda et al., 2014]

Why is poor recruitment a problem?

- The clinical trial sponsor requires a higher power.
- Keep centres open for longer periods.
  - Increased running costs.
  - Apply for additional funding.
- The trial is terminated altogether.
  - Discredits investigators/institutions.

Notation

- C - number of centres,
- τ_c - number of days that centre c has been open,
- $N_c^{(t)}$ - number of arrivals in centre c on day t,
- $N_c^{(\cdot)}$ - number of arrivals in centre c over the whole time period,
- λ_c^0 - rate of arrivals in centre c,
- $g_c(s, \theta)$ - curve shape.

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$$\lambda_c^0 \sim \text{Gam}(\alpha, \alpha/\phi)$$

$$N_c^{(t)} | \lambda_c^0 \sim \text{Pois}\left(\lambda_c^0 \int_{t-1}^{t} g_c(s; \theta)\, \text{d}s\right)$$

Constant Recruitment Rate

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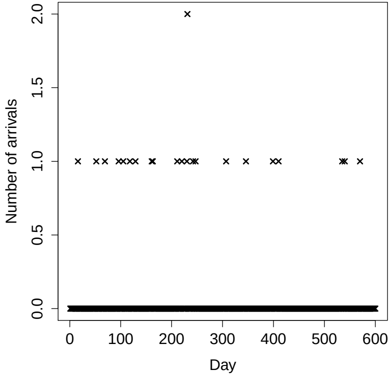
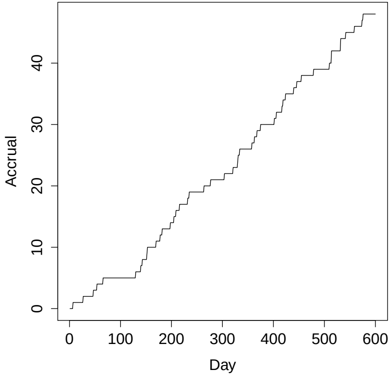




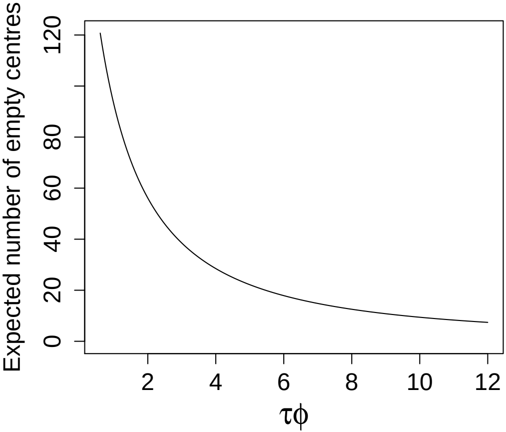
Simulated arrivals with a constant rate for $\alpha = 1.5, \ \phi = 0.2$ and $\tau = 600$.

Constant Recruitment Rate

$$N_c^{(\cdot)} | \lambda_c^0 \sim \text{Pois}\left(\lambda_c^0 \tau_c\right).$$

Anisimov and Federov (2007) assume that:

- The empty centres do not have a substantial effect on the estimation of parameters.
- The recruitment is homogeneous across centres.



Expected number of empty centres against expected number of arrivals in a given centre over the whole time period when $\alpha = 1.5$ and $C = 200$.

The probability of one centre having $n_c^{(\cdot)} \in \mathbb{N}$ recruits across the τ_c days is

$$\mathbb{P}\left(N_c^{(\cdot)} = n_c^{(\cdot)} | \alpha, \phi\right) = \frac{\Gamma\left(\alpha + n_c^{(\cdot)}\right)}{\Gamma(\alpha) n_c^{(\cdot)}!} \left(\frac{\alpha}{\tau_c \phi + \alpha}\right)^{\alpha} \left(\frac{\tau_c \phi}{\tau_c \phi + \alpha}\right)^{n_c^{(\cdot)}}.$$

When $\tau_c = \tau$ for $C = 1, ..., C$, the profile log-likelihood for α can be found with

$$\hat{\phi} = \frac{n_\Sigma}{\tau C} \quad \text{where} \quad n_\Sigma = \sum_{c=1}^{C} n_c^{(\cdot)}.$$

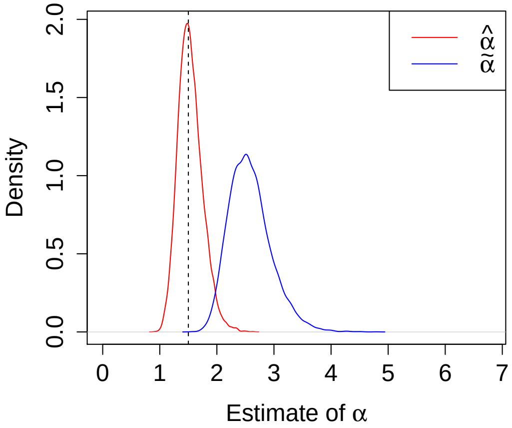
- N_c^+ - only included if $N_c > 0$.
- C^+ - number of non empty centres.

The truncated estimate is

$$\tilde{\phi} = \frac{n_\Sigma^+}{\tau C^+}.$$

The bias of $\tilde{\phi}$ is tractable, we find it to be

$$\begin{aligned}\mathbb{E}[\tilde{\phi}] - \phi &= \frac{\phi \cdot \mathbb{P}(N_c^{(\cdot)} = 0)}{1 - \mathbb{P}(N_c^{(\cdot)} = 0)} \\ &= \frac{\phi \alpha^\alpha}{(\tau\phi + \alpha)^\alpha - \alpha^\alpha}.\end{aligned}$$



Estimates of $\hat{\alpha}$ and $\tilde{\alpha}$ when $\alpha = 1.5,\ \phi = 1/120,\ \tau = 600$ and $C = 200$.

Decaying Recruitment Rate

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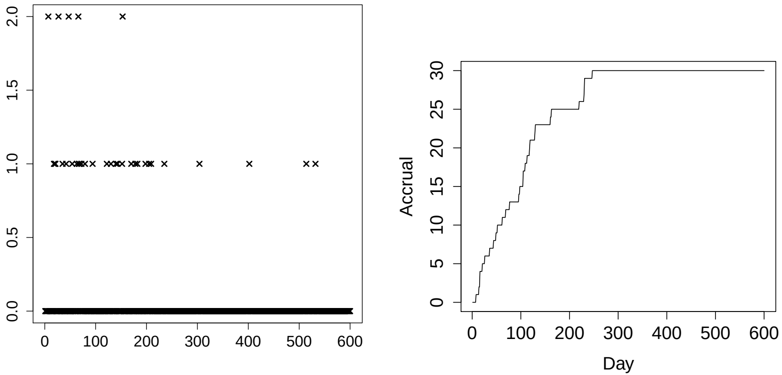


Simulated arrivals with a decaying rate for $\alpha = 1.5, \ \phi = 0.2$ and $\tau = 600$.

Mixed Recruitment Rates

Nonhomogeneous Poisson process:

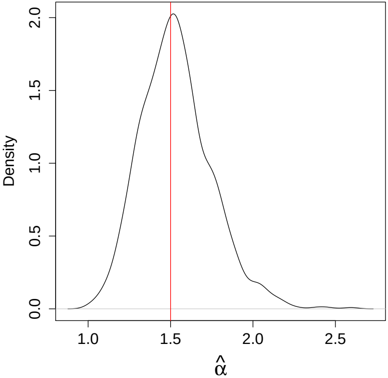
$$N_c^{(t)} | \lambda_c^0 \sim \text{Pois}\left(\lambda_c^0 \int_{t-1}^{t} g_c(s;\theta)\ \text{d}s\right),$$

$$g_c(s;\theta) = \begin{cases} g_0(s;\theta) = 1 & \text{with probability } \eta_0 \\ g_\infty(s;\theta) = \frac{\tau\theta \exp(-\theta s)}{1-\exp(-\theta\tau)} & \text{with probability } \eta_\infty. \end{cases}$$

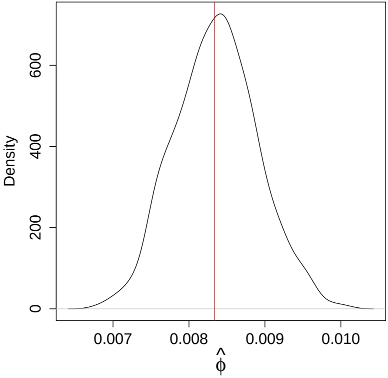
Mixed Recruitment Rates

The probability of one centre having $\mathbf{n}_c$ recruits is

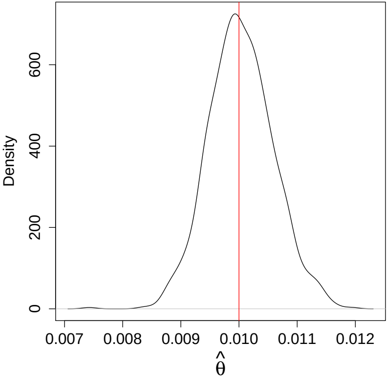
$$\mathbb{P}(\mathbf{N}_c = \mathbf{n}_c | \alpha, \phi, \theta) = \frac{\Gamma\left(\alpha + n_c^{(\cdot)}\right)}{\Gamma(\alpha) \prod_{t=1}^{\tau_c} n_c^{(t)}!} \left(\frac{\alpha/\phi}{\tau_c + \alpha/\phi}\right)^{\alpha} \left(\frac{1}{\tau_c \phi + \alpha/\phi}\right)^{n_c^{(\cdot)}}$$
$$\times \left[\eta_0 \prod_{t=1}^{\tau_c} \int_{t-1}^{t} g_0(s;\theta)\ \mathrm{d}s + \eta_\infty \prod_{t=1}^{\tau_c} \int_{t-1}^{t} g_\infty(\theta; s)\ \mathrm{d}s\right].$$



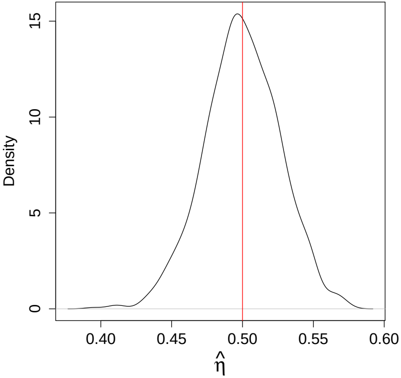
(e) $\alpha = 1.5$



(f) $\phi = 1/120$



(g) $\theta = 0.01$



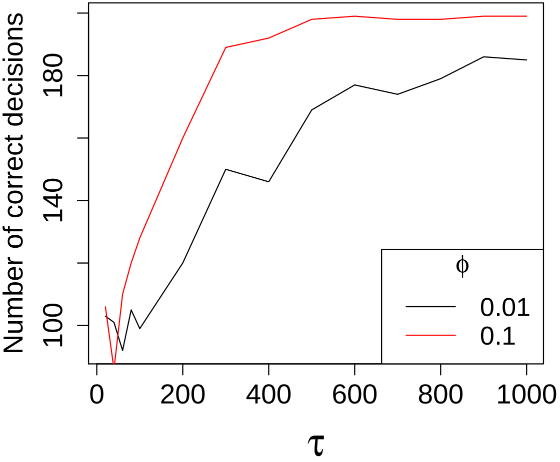
(h) $\eta_0 = 0.5$

Mixed Recruitment Rates

Bayes' Rule:

$$\mathbb{P}(g_c = g_i | \mathbf{n}_c) = \frac{\mathbb{P}(\mathbf{N}_c = \mathbf{n}_c | g_i)\mathbb{P}(g_i)}{\sum_k \mathbb{P}(\mathbf{N}_c = \mathbf{n}_c | g_k)\mathbb{P}(g_k)}.$$

$$\mathbb{P}(g_c = g_i | \mathbf{n}_c) = \frac{\eta_i \prod_{t=1}^{\tau_c} \int_{t-1}^{t} g_i(s;\theta)\ \mathrm{d}s}{\eta_0 \prod_{t=1}^{\tau_c} \int_{t-1}^{t} g_0(s;\theta)\ \mathrm{d}s + \eta_\infty \prod_{t=1}^{\tau_c} \int_{t-1}^{t} g_\infty(s;\theta)\ \mathrm{d}s}$$



Correct classifications for $\alpha = 1.5,\ \theta = 0.01,\ \eta_0 = 0.5$ and $C = 200$.

Conclusions and further work

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- Our method of parameter estimation can identify recruitment trends in individual centres; however, it struggles when we don't have much data.

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Further Work

- Extend to different types of decay and incorporate into one model.
- Consider the case where some centres are open for a different number of days.
- Analyse what happens when we have values of η close to the boundaries of [0,1].

References

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