Modeling Pain score in clinical trials using a joint survival-longitudinal mixed model with a Beta distribution in presence of missing values not occurring at random.

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Modeling Your Drug Development

Introduction

Context

- Trial to assess the efficacy of a drug in patients suffering from **pain**
- Pain is measured by means of a **score** (Likert or VAS) bounded in [0,10].
- **Drop-outs** are frequent in pain trials and are related to the (lack of) efficacy of the drug (from 15% to 35% drop-out)

Objective

Propose a method that allows an unbiased estimation of the treatment effect by:

- Using a longitudinal mixed effect model with a **Beta** distribution (not a Normal or a multinomial one) to model pain score over the duration of the study.
- **Modeling jointly** the pain score and the time to drop-out, with the aim to understand the association between both processes*

*Reference: *« Joint Modelling of longitudinal measurements and event time data »,* Henderson et al. Biostatistics (2000)

Material and methods

- Subject i, $i=1,\ldots,M$, provides:
  - A set of the pain scores: $\{Y_{ij}\ ;\ j=1,\ldots,n_i\}$ at times $\{t_{ij}\ ;\ j=1,\ldots,n_i\}$
  - Drop-out time and indicator (with ST the survival time and C the censored time): $T=\min(ST,C)$ and $\delta = I(ST \leq C) = 1$ for an uncensored observation (drop out occurs) $= 0$ for a censored observation (no drop out)
- Joint distribution of pain scores and event via a latent zero-mean bivariate Gaussian process, realized independenlty:

$$W_i=\{W_{1i}, W_{2i}\}$$

Longitudinal model:

$$Y_{ij} = \mu_i(t_{ij}) + W_{1i} + Z_{ij}$$

- $\mu_i(t_{ij})$ is the mean response
- $Z_{ij} \sim N(0,\sigma_z^2)$ is a sequence of i.i.d. errors
- $W_{1i}=U_{1i}$ with $U_{1i} \sim N(0,\sigma_U^2)$

Survival model:

$$S(t_{ij}) = \exp(-\alpha * t_{ij}) \text{ for exponential function}$$

- $\alpha = \exp(-(\beta_S * dose_i + \mathbf{W_2}))$
- $\mathbf{W_2=\gamma * U_{1i}}$ where γ measures the induced association

=> stochastic dependence

Simulations

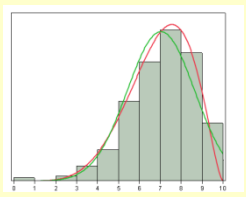
Design : 4 doses (0, 0.75, 2, 4) ; 30 subjects per dose
5 time points: Day 1, 7, 14, 21, 28

Longitudinal class model for estimation (time is a class variable):

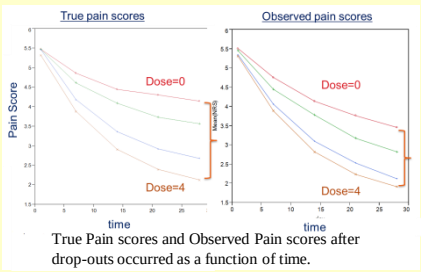
The Beta distribution for Pain score is used with the mean expressed as:

$$\mu = int + base * \beta_{base} + dose*\beta_{dose} + \beta_{t1}*(time=1) + \beta_{t2}*(time=2) + \beta_{t3}*(time=3) + \beta_{t4}*(time=4)$$

Example of simulated data:



Beta distribution (red) vs Normal distribution (green)



True Pain scores and Observed Pain scores after drop-outs occurred as a function of time.

Results

Difference between dose and placebo at Day 28 (True value)	Joint model Mean (SE)	Longitudinal Model Mean (SE)
Dose 0.75 (-0.033)	-0.0325 (0.0047)	-0.0234 (0.0045)
Dose 2 (-0.12)	-0.0867 (0.01272)	-0.0624 (0.0120)
Dose 4 (-0.17)	-0.1734 (0.02544)	-0.1247 (0.0240)

Discussion

- Using the appropriate distribution (i.e. a **Beta** distribution for pain score) is recommended whenever possible to ensure **unbiased** estimates.
- If a **class model** is used to model the pain score, then, ignoring the dropout mechanism provides an underestimation of the treatment effect which can go up to 30% in some situations.
- If the **kinetic** of the pain scores decrease is modeled by, for instance an Emax model, then, ignoring the mechanism of drop-out is less an issue (results not presented).