Statistical testing and Dose-Adaptation simultaneously

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Contents

Preconditions

In this talk:

- Dose adaptation w.r.t. obs. events (e.g. tox. events)
- Define a quantitative criterion (event rate)
- Iterative dose adaptation according to a statistical model
- (Restriction: Events are immediately observable)
- Aim: Combine dose adaptation and inferential statistics

Dose-Adaptation - Method

Model-assumption (Relation: Dose vs. event rate):

$$P(\text{Event=yes}|\text{Dose}) = \frac{\exp(-const. + \theta \text{ Dose})}{1 + \exp(-const. + \theta \text{ Dose})}$$

Aim:

Fix Dose s.t. event rate reaches a desired value, e.g. $P(\text{Event=yes}|\text{Dose}) = 20\%$

Dose-Adaptation - Method

Dose adaptation algorithm:

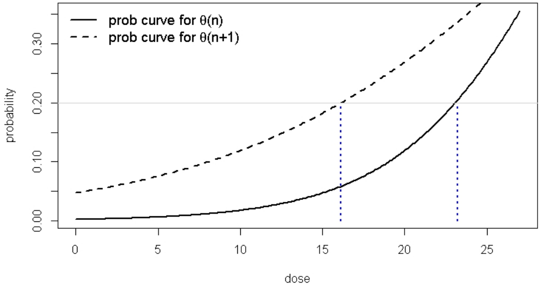
- ML-estimation $\hat{\theta}_1$ for $\theta \longrightarrow$ determines Dose_2 by

$$\frac{\exp(-const. + \hat{\theta}_1 \ \text{Dose}_2)}{1 + \exp(-const. + \hat{\theta}_1 \ \text{Dose}_2)} \stackrel{!}{=} 0.2$$

- Dose_2 for the next patient
- Larger study-population yields improved ML-estimation $\hat{\theta}_2$
- etc. ...

Illustration - Dose-Adaptation

Dose adaptation:



Dose-Adaptation - Method

Relation: Dose vs. estimated distributional parameter:

$$\begin{aligned} \text{Dose}_{i+1} &= \hat{\theta}_i^{-1} \left(\ln(odd(0.2)) + const.\right) \\ &=: \hat{\theta}_i^{-1}\, K \end{aligned}$$

Consider $\hat{\theta}_1, \hat{\theta}_2, \ldots$ and $\text{Dose}_1, \text{Dose}_2, \ldots$ as stoch. processes in time 1,2,...,n,...

Testing Problem

One sample testing problem:

H0: Drug at Tox-Rate 0.2 (Dose_{Limit}) is not more effective than an established drug

vs.

H1: Drug at Tox-Rate 0.2 (Dose_{Limit}) is more effective than an established drug

Virtual Example: Blood Pressure and adverse Effects

From historic data:

Mean blood pressure-decrease C at adverse effect-rate 20% (for an established drug).

Testing problem for a new drug:

$H0$: Mean blood pressure-decrease (at 20% adverse effect-rate) $= C$

vs.

$H1$: Mean blood pressure-decrease (at 20% adverse effect-rate) $> C$

Linear Model

Linear Model-Equation:

$$Y := \beta_1\{\text{Sex=m}\} + ... + \gamma \text{ Dose} + \epsilon$$

where distribution of ϵ does not depend on Dose

Testing problem
(large values for Y correspond to large efficacy):

$$H0 : \gamma \text{ Dose}_{Limit} = C$$

$$vs.$$

$$H1 : \gamma \text{ Dose}_{Limit} > C$$

Value C from literature, historicl data,... etc.

Linear mixed Model

Linear model:

$$\begin{pmatrix} Y_1 \\ \vdots \\ Y_n \end{pmatrix} = \begin{pmatrix} \text{Dose}_1 & X_{11} & \cdots & X_{1p} \\ \vdots & \vdots & \vdots & \vdots \\ \text{Dose}_n & X_{n1} & \cdots & X_{np} \end{pmatrix} \cdot \begin{pmatrix} \gamma \\ \beta_1 \\ \vdots \\ \beta_p \end{pmatrix} + \epsilon$$

respectively

$$\begin{pmatrix} Y_1 \\ \vdots \\ Y_n \end{pmatrix} = \begin{pmatrix} X_{11} & \cdots & X_{1p} \\ \vdots & \vdots & \vdots \\ X_{n1} & \cdots & X_{np} \end{pmatrix} \cdot \begin{pmatrix} \beta_1 \\ \vdots \\ \beta_p \end{pmatrix} + \begin{pmatrix} \gamma \text{ Dose}_1 \\ \vdots \\ \gamma \text{ Dose}_n \end{pmatrix} + \epsilon$$

Linear mixed Model

Relocation:

$$\begin{pmatrix} Y_1 \\ \vdots \\ Y_n \end{pmatrix} = \begin{pmatrix} 1 & X_{11} & \cdots & X_{1p} \\ \vdots & \vdots & \vdots & \vdots \\ 1 & X_{n1} & \cdots & X_{np} \end{pmatrix} \cdot \begin{pmatrix} \gamma \text{ Dose}_{Limit} \\ \beta_1 \\ \vdots \\ \beta_p \end{pmatrix}$$

$$+ \begin{pmatrix} 1 & & 0 \\ & \ddots & \\ 0 & & 1 \end{pmatrix} \cdot \begin{pmatrix} \gamma \left(\text{Dose}_1 - \text{Dose}_{Limit}\right) \\ \vdots \\ \gamma \left(\text{Dose}_n - \text{Dose}_{Limit}\right) \end{pmatrix} + \epsilon$$

Remark: Intercept $= \gamma \text{ Dose}_{Limit}$

Linear mixed Model

Identify linear mixed model:

$$Y = X\beta + Zu + \epsilon$$

Statistical test:

$$\begin{aligned} H0 : \text{Intercept} &= C \\ vs. & \\ H1 : \text{Intercept} &> C \end{aligned}$$

Logistic regression: Distribution of the Estimation-Process

Theory from cumulative parameter estimation processes yields:

$$n(\hat{\theta}_n - \theta) \stackrel{D}{=}_{appr} \frac{B(n)}{const.}$$

Let $\psi(x) := 1/x$. Delta method yields for large n:

$$\begin{aligned}\hat{\theta}_n^{-1} &\stackrel{D}{=}_{appr} -\frac{1}{\theta^2}\frac{1}{const.}\frac{B(n)}{n} + \theta^{-1} \\ &=: \check{\tau}\frac{B(n)}{n} + \theta^{-1}\end{aligned}$$

Logistic Regression: Distribution of the Estimation-Process

Distribution of the process $\hat{\theta}_n^{-1}$:

$$Cov[\hat{\theta}_i^{-1}, \hat{\theta}_j^{-1}] \approx \check{\tau} \, \frac{i \wedge j}{i \, j}$$

respectively:

$$(\hat{\theta}_1^{-1}, ..., \hat{\theta}_n^{-1}) \stackrel{D}{=}_{appr} N(\check{\mu}, \check{\tau}\Sigma)$$
$$\check{\mu} := (\theta^{-1}, ..., \theta^{-1}), \; \Sigma := \left\{ \frac{i \wedge j}{i \, j} \right\}_{i,j=1,...,n}$$

Logistic Regression: Distribution of the Estimation-Process

Distribution of the process Dose_n:

Let $\mu := K\check{\mu}, \tau := K^2\check{\tau}$. Since $\text{Dose}_{i+1} = K\ \hat{\theta}_i^{-1}$

$$(\text{Dose}_2, ..., \text{Dose}_{n+1}) \stackrel{D}{=}_{appr} N(\mu, \tau\Sigma),$$

Linear mixed Model

Linear mixed model-fit:

$$Y = X\beta + Zu + \epsilon$$

with

$$\mathit{shift}(u) \sim N(0, \tilde{\tau}\, \Sigma) \quad \text{and} \quad \Sigma = \left\{ \frac{i \wedge j}{i\ j} \right\}_{i,j=1,\ldots,n}$$

Approach - stoch. differential Equation (SDE)

Modeling SDE for Dose_n in logistic regression model:

- If $\text{Dose}_1, \text{Dose}_2, \ldots \overset{u.i.v}{\sim} F$, then $n(\hat{\theta}_n^{-1} - \theta^{-1}) \overset{D}{=}_{appr} \tilde{\sigma} N(0, n)$
- Inertness of $(\text{Dose}_n - \text{Dose}_{Limit})$ increases with n, drift-impact of an additional subject has approximate weight of $1/n$

$$d(n\,(\text{Dose}_n - \text{Dose}_{Limit})) =_{H0} -\tau\,(\text{Dose}_n - \text{Dose}_{Limit})dn + \sigma\; dB(n)$$

Approach - stoch. differential Equation (SDE)

Solution:

$\text{Dose}_n - \text{Dose}_{Limit}$ centered gaussian process with covariance structure:

$$\Sigma = \left\{ \tilde{\tau} \, \frac{i \wedge j}{i \, j} \left(\frac{i \wedge j}{i \vee j} \right)^{\tau} \right\}_{i,j=1,\ldots,n}$$

Forthcoming

- Extension to Coxregression
- Powercalculation
- Problem: Immediately observable events
- Implementation of further dose adaptation-strategies
- Software implementation