Investigations on Stochastic Calculus,
Statistics of Processes
Applied Statistics for Biology and Medical Research

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B- Applied statistics for Biology and Medical Research

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7. Elements for analysing mediation and evolution in Epidemiology
8. Various results in interaction with Biology

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Definition (Filtered Processes)

Class of stochastic processes defined by:

$$\left\{ X_t^K = \int_0^t K(t,s)\, \mathrm{d}X_s \; : \; t \in [0,T] \right\}$$

where

- X is the so-called underlying process
  - Brownian motion, Poisson process or Lévy process
- K is a deterministic kernel
  - Triangular ($K(t,s) = 0$ as soon as $s > t > 0$)

- Covers a wide range of classic stochastic processes (Fractional Brownian motion, Shot noise processes,...)
- Integrates correlation in increments in standard settings

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Aims: Define an integral with respect to Filtered Processes

Problems: In general not a Martingale nor a Markov process

A solution: Define integrals by means of Malliavin Calculus

The ingredients (for a process X):

- $\mathcal{S}^X$ a dense subset of $\mathbb{L}^2(\Omega)$ w.r. to an inner product $<,>_X$
- D^X called stochastic gradient defined on $\mathcal{S}^X$ its domain $\mathbb{D}^{1,2,X}$

Definition

A process $u \in \text{Dom}(\delta^X)$ if there exists a constant $C(u)$ s.t.

$$\left|\mathbb{E}\left[\langle \mathrm{D}^X F, u\rangle_H\right]\right| \leq C(u)\|F\|_{L^2(\Omega)} \qquad \text{for any } F \in \mathbb{D}^{1,2,X} \qquad (1)$$

$F \to \langle \mathrm{D}^X F, u\rangle_H$ is continuous, there exists $\delta^X(u)$ such that:

$$\mathbb{E}\left[F\,\delta^X(u)\right] = \mathbb{E}\left[\langle \mathrm{D}^X F, u\rangle_H\right] \qquad \text{for any } F \in \mathbb{D}^{1,2,X} \qquad (2)$$

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- Relevant choices of $(\mathcal{S}^X, D^X)$ allow to interpret δ^X as an integral: **Skohorod integral**
  - For deterministic u, $\delta^X(u)$ coincides with X-Wiener integral
  - For predictable u, $\delta^X(u)$ coincides with Itô integral

This strategy is possible for X a
  - Brownian motion
  - filtered Brownian motion
  - standard Poisson process
  - marked Poisson process
  - Lévy process

- δ^X_C construct by means of
  - $\mathcal{S}^X$ comes from chaos expansion of a r.v.
  - D^X is the chaos annihilation operator
- δ^X_G construct by means of
  - $(\mathcal{S}^X, D^X)$ are cylindrical variables and "true" stochastic gradient

No direct approach for filtered Poisson and filtered Lévy processes

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  - standard Poisson process (Nualart, Vives (1990))
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  - Lévy process (Solé, Utzet, Vives (2007))
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No direct approach for filtered Poisson and filtered Lévy processes

First approach: Directly

Available only for filtered Brownian motion

Second approach: Use of an operator

One can construct an operator $\mathcal{K}^*$ such that

$$\mathcal{K}^*(\,\mathbb{I}_{[0,t]}) = K(t,\cdot)\;\mathbb{I}_{[0,t]} \tag{3}$$

One can construct integrals w.r.t. to X^K by means of integrals w.r.t. to X:

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$$X_t^K = \int_0^t K(t,s)\, dX_s$$

Third approach: Use of an integral operator - $\mathcal{S}$-transform

- In the Brownian setting $X \equiv B$
  - (Bender (2003))
- In the (marked) Poisson setting $X \equiv N$
  - (Bender, Marquart (2008))
- In Lévy setting $X \equiv L$
  - (**Savy**, Vives (2014))

Conclusions:
We can define many integrals for filtered Poisson processes

- Are these definitions equivalent ?
- How they behave with Lévy-Itô decomposition $L = B + J$?

$$\delta^L(u) = \delta^B(u) + \delta^J(u)$$

- Are the components $\delta^B(u)$ and $\delta^J(u)$ still independent ?

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Results (**Savy**, Vives (2014))

Defined by the use of	$X = L$	$X = B$	$X = J$	LIP true	LIP Ind.
Intrinsic Chaos		$\delta_C^{B,K}$		-	-
Intrinsic $\mathcal{S}$-transform	$\delta_S^{L,K}$	$\delta_S^{B,K}$	$\delta_S^{J,K}$		
$\mathcal{K}^*$ and Chaos	$\delta_C^{L,\mathcal{K}^*}$	$\delta_C^{B,\mathcal{K}^*}$	$\delta_C^{J,\mathcal{K}^*}$		
$\mathcal{K}^*$ and $\mathcal{S}$-transform	$\delta_S^{L,\mathcal{K}^*}$	$\delta_S^{B,\mathcal{K}^*}$	$\delta_S^{J,\mathcal{K}^*}$		

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Defined by the use of	$X = L$	$X = B$	$X = J$	LIP true	LIP Ind.
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Remark

What about integrals defined by "true" stochastic gradient ?

- *In the Brownian case* $\delta_G^B = \delta_C^B$
- *Even in standard Poisson setting* $\delta_G^J(u) \neq \delta_C^J(u)$

LDP and SLDP for O-U processes

- Consider a fractional Ornstein Uhlenbeck process:

$$\begin{cases} dX_t &= \theta X_t dt + dB_t^H \\ X_0 &= 0 \end{cases} \tag{4}$$

- Consider the **MLE of θ** associated to (4)

$$\widehat{\theta}_T = \frac{\text{"} \int_0^T X_t \, dX_t \text{"}}{\int_0^T X_t^2 \, dt} \tag{5}$$

Theorem

- ***Strong Law of Large Number:*** $\widehat{\theta}_T \xrightarrow[T\to\infty]{a.s.} \theta$
- ***Central Limit Theorem*** *in the stable case* ($\theta < 0$)

$$\sqrt{T}(\widehat{\theta}_T - \theta) \xrightarrow[T\to\infty]{\mathcal{L}} N(0, -2\theta)$$

- ***Central Limit Theorem*** *in the unstable case* ($\theta > 0$)

$$\exp(\theta T)(\widehat{\theta}_T - \theta) \xrightarrow[T\to\infty]{\mathcal{L}} 2\theta C \quad \text{where } C \text{ is Cauchy}$$

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- Consider a fractional Ornstein Uhlenbeck process:

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Asymptotic behaviour of $(\widehat{\theta}_T)$ in terms of **Large Deviation Principle**

Definition

- A family of random variables (Z_T) satisfies a **LDP** of good rate function I if there exists a function I l.s.c. from $\mathbb{R}$ to $[0, +\infty]$ s.t.

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$$\left\{\widehat{\theta}_T \leq c\right\} \Longleftrightarrow \left\{\frac{\text{"}\int_0^T X_t\, dX_t\text{"}}{\int_0^T X_t^2\, dt} \leq c\right\} \Longleftrightarrow \{Z_T(a,c) \leq 0\}$$

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$$I(c) = -\inf_{a \in \overline{\Delta_c}} \mathcal{L}(a) \tag{6}$$

and denote $a_c = \operatorname{argmin}_{a \in \overline{\Delta_c}} \mathcal{L}(a)$ (7)

Lemma

- *The limit $\mathcal{L}$ of $\mathcal{L}_T$ is*

$$\mathcal{L}(a) = -\frac{1}{2}(a + \theta + \varphi(a))$$

with

$$\varphi(a) = \begin{cases} \sqrt{\theta^2 + 2ac} & \textbf{for } (\theta < 0) \\ -\sqrt{\theta^2 + 2ac} & \textbf{for } (\theta > 0) \end{cases}$$

- *its domain Δ_c is*

$$\left\{ a \in \mathbb{R} \text{ s.t. } \theta^2 + 2ac > 0 \text{ and } \sqrt{\theta^2 + 2ac} > \max(a+\theta; -\delta_H(a+\theta)) \right\}$$

Theorem (Stable setting $\theta < 0$)

The sequence $(\widehat{\theta}_T)$ satisfies an **LDP** *with rate function*

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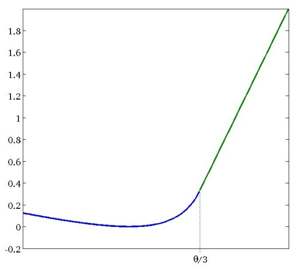

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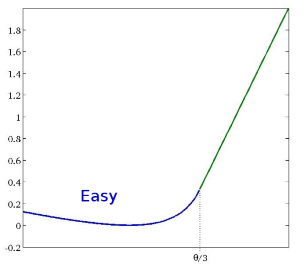

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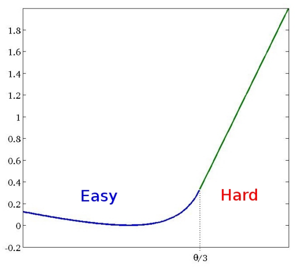

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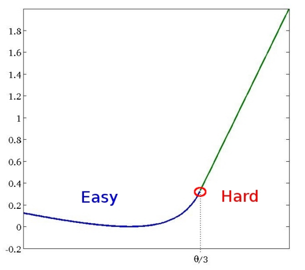

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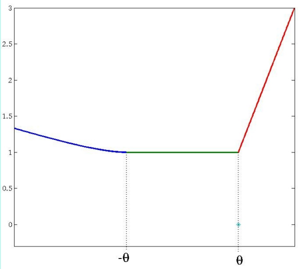

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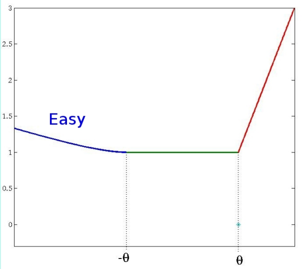

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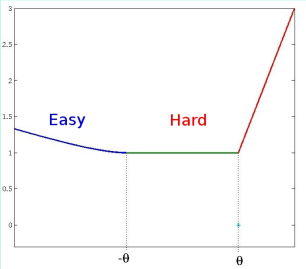

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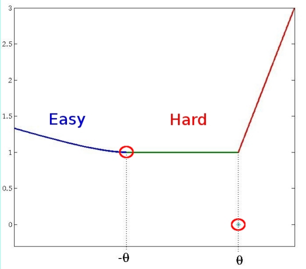

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Lemma

For any a in the interior of Δ_c, we have the expansion :

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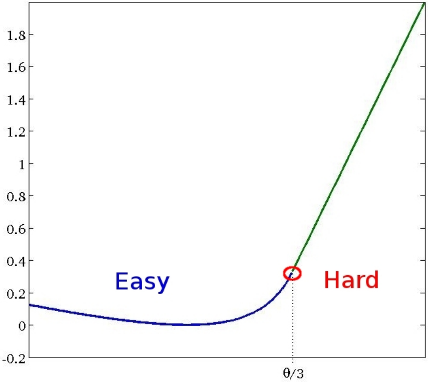
Stable Case



Theorem (Setting ($\theta < 0, H = \frac{1}{2}$) - (Bercu, Rouault (2002)))

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  where $\tau_\theta = (-\theta/3)^{1/4}/\Gamma(1/4)$.

- ***For*** $c = 0$, *it exists a sequence* (b_k) *such that, for any* $p \geq 1$ *and* T *large enough*

$$\mathbb{P}\left[\widehat{\theta}_T \geq 0\right] = \frac{\exp(\theta T)}{\sqrt{\pi}\sqrt{-\theta}}\frac{1}{\sqrt{T}}\left[1+\sum_{k=1}^{p}\frac{b_k}{T^k}+\mathcal{O}\left(\frac{1}{T^{p+1}}\right)\right].$$

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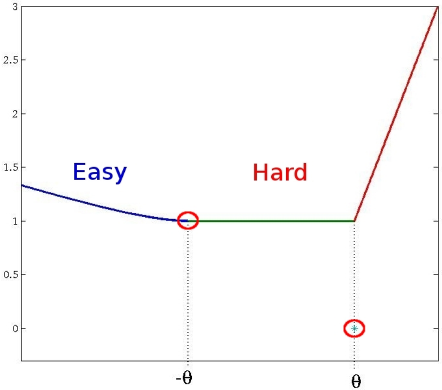
Unstable Case



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The **recruitment period** is the duration between the initiation of the first of the C investigator centres and the instant $T(N)$ when the N patients are included.

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  - The duration of the recruitment period is very **hard to control**
  - A clinical trial is **expensive**
    - $ 150.000.000: Average out-of-pocket clinical cost for each new drug
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- **What a model of recruitment for ?**
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    - based on the estimation of $T(N)$ (punctually and by means of CI)
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Queueing theory		**Clinical research**
Storage capacity	$\longleftrightarrow$	target population or cohort
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Consider a multicentric trial involving C investigator centres

- N: number of patients to be recruited
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  $\Longrightarrow$ **modelled by a PP of rate** λ_i
- $\mathcal{N}$: the global recruitment process

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  $\Longrightarrow$ **is the stopping time** $\inf\{t \in \mathbb{R} \,|\, \mathcal{N}(t) \geq N\}$
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- ***If λ is known (given by the investigator)*** *then*

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$$\mathbb{P}\left[\mathcal{N}(T_R) \geq N \mid \mathcal{F}_{T_1}\right]$$

$$= 1 - \sum_{k=0}^{N-N_1-1} \frac{1}{k!} \int_{\mathbb{R}^C} \left(\int_{T_1}^{T_R} (x_1 + \ldots + x_C) dt\right)^k e^{-\int_{T_1}^{T} (x_1+\ldots+x_C)dt} \prod_{i=1}^{C} p_\lambda^{T_1}(x_i)\, dx_i \qquad (8)$$

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$$\mathbb{E}\left[\inf_{t\in\mathbb{R}} \{\mathcal{N}(t) \geq N\} \mid \mathcal{F}_{T_1}\right] = N \int_{\mathbb{R}^C} \frac{p_\lambda^{T_1}(x_1, \ldots, x_C)}{x_1 + \ldots + x_C} dx_1 \ldots dx_C \qquad (9)$$

  Involving $p_\lambda^{T_1}$ *the forward density of* λ.

- ***If λ is unknown*** *then*
  - $\hat{\lambda}$ *an estimation of* λ *from the data collected on* $[0, T_1]$
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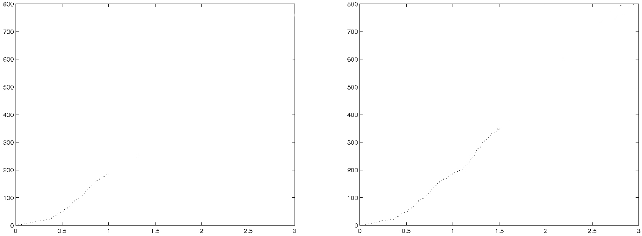
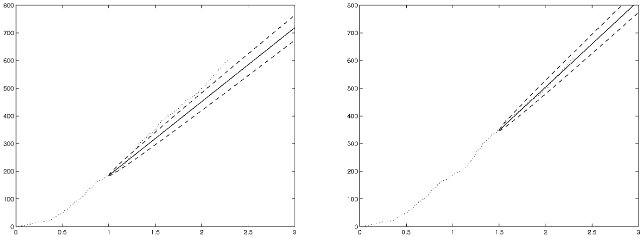


Figure: On going study at 1 year (on the left) and at 1.5 year (on the right)

- Dots: Real data used to calibrate the model



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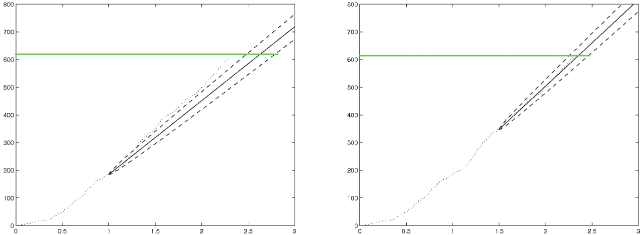
The recruitment process model

On-going studies



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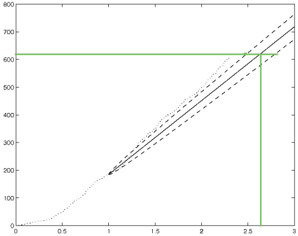

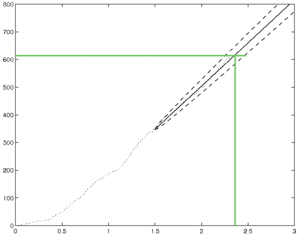

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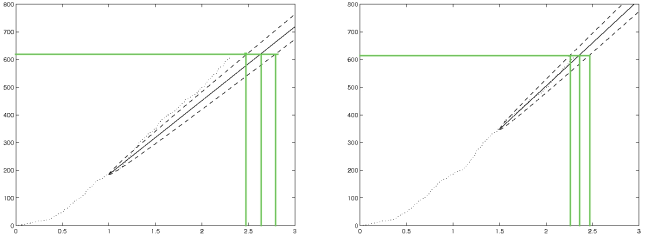

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Limit of this approach

Problem 1: If p estimations are needed to describe $\mathcal{N}_i$, $C \cdot p$ estimation are needed to describe $\mathcal{N}$

When C large, this is not relevant

Problem 2 : If centre i has not recruited before T_1, then $\hat{\lambda}_i = 0$ and the model does not authorize centre i to recruit later

Empirical Bayesian model

Ones considers

$$(\lambda_1, \ldots, \lambda_C)$$

is a sample of size C distributed by a certain distribution $\mathcal{L}(\theta)$

Instead of estimate C values of λ, one estimates θ

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- **Objectives:**
  - $N = 610$ patients
  - $T_R = 3$ years
  - $C_R = 77$ investigators centres
- **On-going studies:** after 1 year, after 1.5 year and after 2 years
- **The estimated duration** of the trial

The model	Time 1	Time 1.5	Time 2
Constant intensity	3.30	2.63	2.44
Γ-Poisson model	3.31	2.63	2.44
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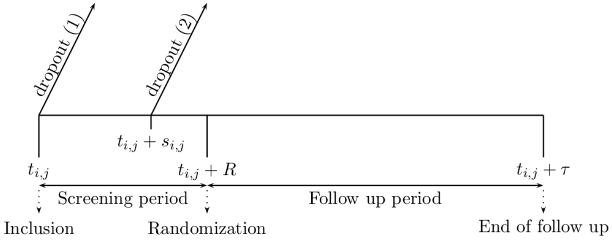

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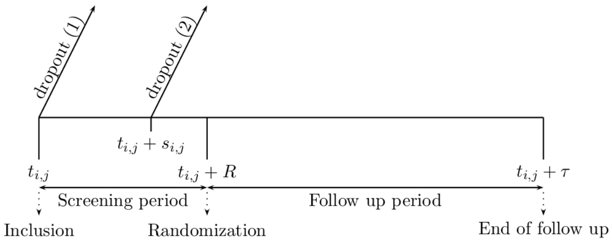

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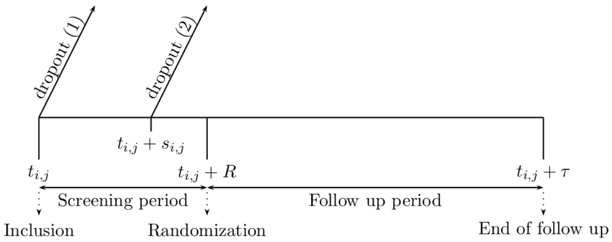

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- The recruitment dynamic is $\Gamma(\alpha, \beta)$-Poisson.
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Given data $\{(n_i, r_i, \tau_i), 1 \leq i \leq C\}$, the log-likelihood function writes:

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Given data $\{(n_i, r_i, \tau_i, \nu_i),\ 1 \leq i \leq C\}$, the predicted process of the number of randomized patients in centre i, $\{\widehat{\mathcal{R}}^i(t),\ t \geq T_1 + R\}$, expenses as

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- The inclusion process $\mathcal{N}_i$ is modelled by a **PP(λ_i)**
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Improvement of patient recruitment' models

An additive model for cost

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    - g_i is a triangular function $g_i(t,s) = 0$ when $t \le s$
    - T_j^i are randomization time of the patient j by centre i

Consider a clinical trial such that for centre i,

- The inclusion process $\mathcal{N}_i$ is modelled by a **PP(λ_i)**
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- The duration of the trial is the stopping time

$$T(N) = \inf_{t \ge 0} \{\mathcal{R}(t) \ge N\}$$

- The total cost of the trial is thus $\mathcal{C}(T(N)) = \sum_{i=1}^{C} \mathcal{C}_i(T(N))$
- In order to compute $\mathcal{C} = \mathbb{E}\left[\mathcal{C}(T(N))\right]$ we have to compute

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- *Assume $(\lambda_i)_{1\leq i\leq C}$ and $(p_i)_{1\leq i\leq C}$* ***are known***

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Habilitation thesis defence
Stochastic Calculus
Anticipative Integrals and Malliavin Calculus
LDP and SLDP for Ornstein-Uhlenbeck processes
Applied Statistics for Medical Research
Recruitment modelling
Survival data analysis
Conclusions and Perspectives

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Assume the closure of centre j, denote

- $T^j(N)$ the duration of the trial without centre j
- $\mathcal{C}^j(t)$ the cost of the trial at time t without centre j

- By means of Monte Carlo simulation we are able to evaluate the variation of cost due to centre j closure:

$$\Delta\mathcal{C}_j = \mathbb{E}\left[\mathcal{C}(T(N)) - \mathcal{C}^j(T^j(N))\right]$$

- Consider $(\Delta\mathcal{C}_j, T^j(N))$ to decide on the closure of centre j.

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- The GuidAge Trial
  - Double blind controlled randomized trial
  - 240 mg per day of de Ginkgo Biloba versus placebo
  - G.B. appears **to delay the conversion** to dementia of Alzheimer type
  - Primary endpoint: conversion to Alzheimer disease (time to event)

- **Statistical Analysis Plan:** Logrank test

  Conclusion: P-value 0.3044

  No Significant effect of the treatment

- **Re-analysis:** Fleming-Harrington's test ($q = 3$)

  Conclusion: P-value 0.0041

  Significant effect of the treatment

- **Is logrank test relevant for such a prevention study ?**

- D: the time to event random variable
  - F: the distribution function associated to D
  - $S = 1 - F$: the survival function associated to D
  - λ: the risk function associated to D
- Subjects may be right-censored by C independent of D.
  - $X_i = D_i \wedge C_i$: observed data
  - $\delta_i = \mathbb{I}_{\{D_i \leq C_i\}}$: censoring indicator
- $N_n(t)$: Number of events observed at time t:

$$N_n(t) = \sum_{i=1}^{n} \mathbb{I}_{\{X_i \leq t, \delta_i = 1\}}$$

- $Y_n(t)$: Number of at risk subjects at time t:

$$Y_n(t) = \sum_{i=1}^{n} \mathbb{I}_{\{X_i \geq t\}}$$

We aim to test:

$$\mathcal{H}_0 : S^P(t) = S^T(t),\ \forall t$$
$$\mathcal{H}_1 : S^P(t) \neq S^T(t)$$

S^P and S^T are the survival functions associated respectively to the Placebo arm and Treatment arm.

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Logrank test defined as:

$$\mathrm{LR}_{W_n}(t) = \int_0^t \sqrt{\frac{n_P + n_T}{n_P n_T}} \frac{Y^P_{n_P}(s) Y^T_{n_T}(s)}{Y^P_{n_P}(s) + Y^T_{n_T}(s)} \left[\frac{dN^P_{n_P}(s)}{Y^P_{n_P}(s)} - \frac{dN^T_{n_T}(s)}{Y^T_{n_T}(s)} \right]$$

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Weighted Logrank test defined as:

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W_n is an adapted, positive, predictable process

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W_n is an adapted, positive, predictable process

The $\mathcal{H}_1$ assumption detected by the test depends on the weight

- **Constant piecewise weight**

$$W(t) = \begin{cases} 0 & \text{if} \quad t < t^* \\ 1 & \text{if} \quad t > t^* \end{cases}$$

Easy to interpret: t^* beginning of effect

- **Fleming Harrington weight** for late effect detection

$$W_n(t) = (1 - \widehat{S}_n(t))^q$$

where $\widehat{S}_n$ is the Kaplan-Meier estimator of S under the $\mathcal{H}_0$

Classical test but hard to interpret: what is the role of q ?

- Application of Fleming-Harrington's test in a Clinical trial setting
  - Wa have to choose a value for parameter q
  - We have to compute the necessary sample size

  (Garès, Andrieu, Dupuy, **Savy** (submitted to JRSS-C 2014))

- Comparison of CPWL test and Fleming Harrington's test
  - Comparison of performances
  - Bridge between the parameters of each test

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  - To evaluate the performance of a test
  - To compare tests

- **Strategy:**
  - Make use of the **Asymptotic (Relative) Efficiency** (Van der Vaardt (1998))
  - There exists several notions of ARE
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$$\begin{cases} \mathcal{H}_0 & : \lambda^T = \lambda^P = \lambda_{\theta_0}, \\ \mathcal{H}_1 & : \lambda^T = \lambda_{\theta^T} \quad \text{and} \quad \lambda^P = \lambda_{\theta^P} \end{cases}$$

Theorem

- ***Under*** $\mathcal{H}_0$ ***:***

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Asymptotic normality of WLT

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$$\begin{cases} \mathcal{H}_0 & : \lambda^T = \lambda^P = \lambda_{\theta_0}, \\ \mathcal{H}_1 & : \lambda^T = \lambda_{\theta^T} \quad \text{and} \quad \lambda^P = \lambda_{\theta^P} \end{cases}$$

Theorem

- ***Under*** $\mathcal{H}_0$***:***

$$\mathrm{LR}_{W_n} \xrightarrow[n\to+\infty]{\mathcal{L}(\mathbb{D})} \mathbb{G}_0$$

  - $\mathbb{G}_0$ *centred Gaussian process of covariance function* $\Sigma_0(w, \lambda_{\theta_0})$
- ***Under*** $\mathcal{H}_1$ ***:***

$$\mathrm{LR}_{W_n} - \sqrt{n}\,\mu_{(\theta^P,\theta^T)} \xrightarrow[n\to+\infty]{\mathcal{L}(\mathbb{D})} \mathbb{G}_1$$

  - $\mathbb{G}_1$ *centred Gaussian process of covariance function* $\Sigma_1(w, \lambda_{\theta^P}, \lambda_{\theta^T})$
  - $\mu_{(\theta^P,\theta^T)}$ *is function of* w, λ_{θ^P} *and* λ_{θ^T}

The idea is to consider the assumptions

$$\begin{cases} \mathcal{H}_0 & : \ F^T = F^P = F_{\theta_0}, \\ \mathcal{H}_1 & : \ F^T = F_{\theta^T_{n_T}} \quad \text{and} \quad F^P = F_{\theta^P_{n_P}} \end{cases}$$

in such a way that

- **The class of assumptions is sufficiently wide**

$$F_\theta(t) = \Psi(g(t) + \theta), \qquad \theta \in \Theta$$

- Ψ a distribution function with continuous second derivative
- g an increasing differentiable function

- **Choosing**

$$\theta_{n_P}^{P} = \theta_0 + c\sqrt{\frac{n_T}{n_P(n_P+n_T)}} \quad \text{and} \quad \theta_{n_T}^{T} = \theta_0 - c\sqrt{\frac{n_P}{n_T(n_P+n_T)}}$$

the singularity vanishes:

$$\sqrt{n}\,\mu_{(\theta_{n_P}^{P},\theta_{n_T}^{T})} \xrightarrow[n\to\infty]{a.s.} \mu_{\theta_0}$$

- **The efficiency of the test** can be measure by means of Pitman's **Asymptotic Efficiency**

$$AE = \frac{(\mu_{\theta_0}(\tau))^2}{\Sigma_0(\tau,\tau)}$$

- **Asymptotic Efficiency** depends on
  - the weight
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Theorem ((Garès, Dupuy, Andrieu, **Savy** (JRSS-C 2014)))

Given a

- *a shift* Δ
- *a constant* $\lambda_0 > 0$
- *a parameter* $q > 0$

there exists a function $\Gamma^q(\cdot, \lambda_0, \Delta)$ *such that the Fleming-Harrington test* $\mathrm{FH}(q)$ *has* ***maximum Asymptotic Efficiency*** *to test*

$$\begin{cases} \mathcal{H}_0 & : \ \lambda^P = \lambda_0, \\ \mathcal{H}_1 & : \ \lambda^T = \lambda_0 \, \Gamma^q(\cdot, \lambda_0, \Delta) \end{cases} \tag{10}$$

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Study the performance of $\mathrm{FH}(q)$ **thanks to simulation study**

- **Parameters (usually given by investigator)**
  - the sample size n
  - $c = S^P(\tau)$
  - $S^T(\tau)$ or discrepancy rate $r = \frac{S^T(\tau) - S^P(\tau)}{1 - S^P(\tau)}$
- **The data in the placebo group**
  - Simulated from an exponential distribution with parameter $\lambda_0 > 0$
  - λ_0 is given by the desired proportion of censored data:

$$\lambda_0 = -\frac{\ln(S^P(\tau))}{\tau}$$

- **The data in the treatment group**
  - Fix $q_S > 0$
  - Compute $\Delta(q_S)$
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$$\lambda^T(t) = \lambda_0 \, \Gamma^q(\cdot, \lambda_0, \Delta(q_S))$$

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q_S	Logrank	$q_T = 1$	$q_T = 2$	$q_T = 3$	$q_T = 4$
0	**0.640**	0.534	0.420	0.349	0.294
1	0.620	**0.743**	0.713	0.670	0.632
2	0.609	0.845	**0.877**	0.871	0.853
3	0.593	0.873	0.912	**0.914**	**0.914**
4	0.587	0.887	0.940	0.957	**0.961**
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Table: Empirical power of FH(q_T) under scenarios $\mathcal{S}_1(q_S, 2000, 0.2, 0.8)$

Main result (Garès, Dupuy, Andrieu, **Savy** (JRSS-C 2014))

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Comparison Fleming Harrington and CPW logrank tests

- CPWL depends on a parameter t^*
- This parameter has a concrete reality (beginning of the effect)

The strategy:

- Find the assumptions under which CPWL(t^*) is optimal

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Main result (Garès, Dupuy, Andrieu, **Savy** (EJS 2014))

- CPWL(t^*) test exhibits little sensitivity to the value of t^*
- FH(q) is less sensitive to q than the CPWL(t^*) is to t^*
- Given t^*, it is possible to find the value of $q(t^*)$ which maximizes

$$\mathrm{ARE}(\mathrm{FH}(q(t^*)), \mathrm{CPWL}(t^*))$$

CPWL(t^*)	$t^* =$	0.2	0.4	0.6	0.8
FH($q(t^*)$)	$q(t^*) =$	0.5	1.2	2.4	5.9
FH(q)	$q =$	1	2	3	4
CPWL($t^*(q)$)	$t^*(q) =$	0.3	0.5	0.6	0.7

Table: Correspondence between q and t^*.

A versatile test

- Fleming-Harrington's test is a good test when late effects exist
- Logrank's test is a good test when effects are constant in time

  Investigators do not want to bet on a situation rather than another

- In (Garès, Dupuy, Andrieu, **Savy** (SIM 2014)), we introduce MWL statistics

$$\mathrm{MWL}^{\vec{q}}(t) = \max_{i=1,\dots,m}\left(\left|\frac{\mathrm{FH}^{q_i}(t)}{\widehat{\sigma}_{q_i}(t)}\right|\right)$$

- For $i = 1, \dots, m$, assume given p_i the probability that late effect of "type q_i" occurs (**expert a priori**)
- We investigate its performances for testing

$$\begin{cases} \mathcal{H}_0 & : F^T = F^P = F, \\ \mathcal{H}_1 & : \cup_{i=1}^{m} \{F^T = \Psi^{q_i}(g + \theta^T(i)) \text{ and } F^P = \Psi^{q_i}(g + \theta^P(i))\} \end{cases}$$

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Main result (Garès, Dupuy, Andrieu, **Savy** (SIM 2014))

- Computation of asymptotic distributions under $\mathcal{H}_0$ and $\mathcal{H}_1$
- Procedure for NSS computing
- **Good power** even when far from the optimal assumption

q_S	LR	FH^1	FH^2	FH^3	FH^4	FH^5
0	**0.629**	0.526	0.416	0.334	0.289	0.256
1	0.625	**0.756**	0.744	0.702	0.655	0.611
2	0.609	0.839	**0.864**	0.863	0.850	0.835
3	0.623	0.869	0.919	**0.925**	0.922	0.910
4	0.626	0.891	0.943	0.959	0.961	**0.963**
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q_s		MWL^1	MWL^2	MWL^3	MWL^4	MWL^5
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2		0.797	**0.828**	0.826	0.816	0.801
3		0.833	0.881	**0.897**	0.896	0.888
4		0.864	0.923	0.936	**0.946**	0.945
5		0.880	0.947	0.959	0.967	0.968

where $MWL^q = MWL^{(0,q)}$ with $p(q) = \frac{1}{2}$

An "omnibus" test

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- Computation of asymptotic distributions under $\mathcal{H}_0$ and $\mathcal{H}_1$
- Procedure for NSS computing
- **Good power** even when far from the optimal assumption

q_S	LR	FH^1	FH^2	FH^3	FH^4	FH^5
0	**0.629**	0.526	0.416	0.334	0.289	0.256
1	0.625	**0.756**	0.744	0.702	0.655	0.611
2	0.609	0.839	**0.864**	0.863	0.850	0.835
3	0.623	0.869	0.919	**0.925**	0.922	0.910
4	0.626	0.891	0.943	0.959	0.961	**0.963**
5	0.608	0.911	0.963	0.976	0.978	**0.982**
q_s		MWL^1	MWL^2	MWL^3	MWL^4	MWL^5
0		**0.620**	0.606	0.589	0.584	0.582
1		0.729	**0.731**	0.720	0.692	0.679
2		0.797	**0.828**	0.826	0.816	0.801
3		0.833	0.881	**0.897**	0.896	0.888
4		0.864	0.923	0.936	**0.946**	0.945
5		0.880	0.947	0.959	0.967	0.968

where $\mathrm{MWL}^q = \mathrm{MWL}^{(0,q)}$ with $p(q) = \frac{1}{2}$

An "omnibus" test

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    - **SMPR** - Principal Investigator - IRESP (plan cancer) 2013-2015
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  - How to model the whole clinical trial ?
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