# A joint dynamic hierarchical multi-state model.

Pamela Chiroque Helio S. Migon

Universidade Federal do Rio de Janeiro

June 8, 2017

# Motivation

Simultaneous analysis of quality of life and survival data

# Review

- Ghosh e Mukhopadhyay (2007), proposed a Bayesian Analysis of Quality Adjusted Lifetime (QAL) Data;
- Silva et al. (2009), developed semi-Markov multistate model for estimation of the mean quality-adjusted survival for non-progressive processes.

# Review

## Drawback

- The health state unknown;
- The health status transition information and duration of health status may not available;
- The health status transition is progressive.
- Independence from previous states
- Sojourn time of each health state within partitioned intervals (mean).

# Joint models for longitudinal and survival data

Wulfsohn e Tsiatis (1997), Henderson et al. (2000), Brown e Ibrahim (2003), Gou e Carlin (2004), Rizopoulos (2012)

## Intuitive idea behind these models

- Use an appropriate model to describe the evolution of the marker in time for each patient;
- the estimated evolutions are then used in a relative risk model (parametric or semi parametric approach).

# Joint models for longitudinal and survival data with structural change

**Problem**

Modeling time-to-event data and repeated measurements influenced by structural change.

# Proposal

## A joint hierarchical dynamic models (hdc) with structural change

- Included structural change based on Kim e Nelson (1999).
  - The survival model incorporate longitudinal information into the design of a time to-event study.
  - Incorporate health status non-progressive.

# Specifics objectives I

- Estimates of the transition probabilities;
- Reduce bias in the estimates of the overall treatment effect,that is,the treatment effect on survival and the longitudinal marker;
- Estimates of the relative risk including structural change.

# DAG: Joint hierarchical dynamic models (hdc) with structural change model

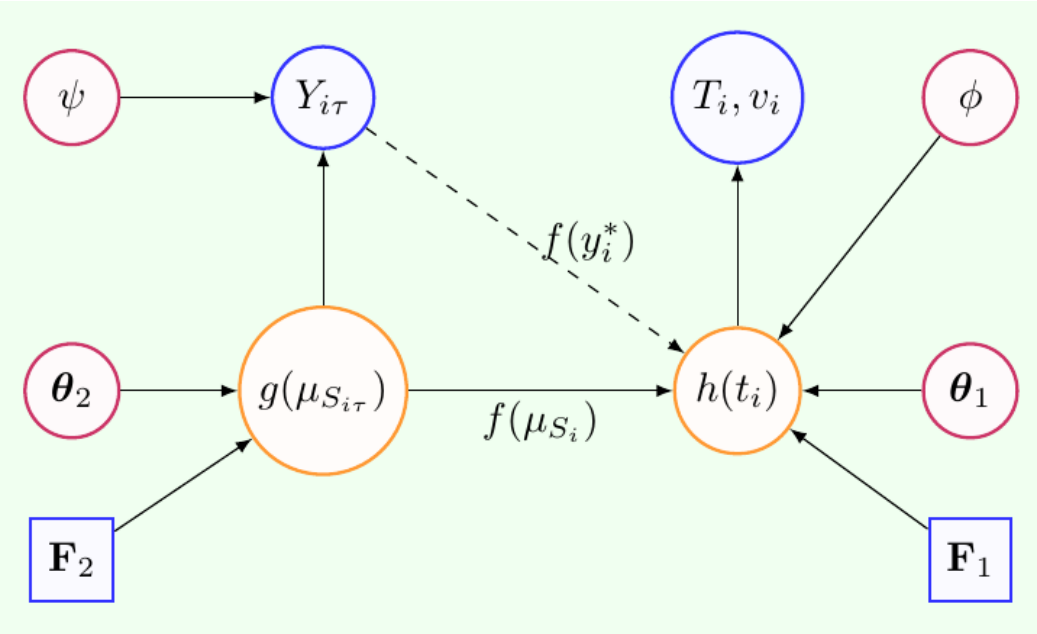



Figure: $Yi\tau$ longitudinal component; $\mu_{S_{ij}}$ trajectory function; the relative risk $h(t_i)$; $\boldsymbol{F}$ covariates; $S_{ij}$ latent status.

# Notation

## Information: $\{\boldsymbol{Y}_i, T_i, v_i, \mathbf{Z}_i, \quad i = 1, \ldots, n\}$

$n$ subjects, indexed by $i$ each of whom has $J$ observations of a marker of disease progression

- $\boldsymbol{Y}_i = \{y_{ij}, \quad j = 1, \ldots, J\}$, where $y_{ij}$ is the observed outcome for the i*th* subject at the j*th* time point. Possible with missing values, on date $\tau_j$, with relation $0 \leq \tau_1 < \tau_2 < \ldots < \tau_J$, such as, $\tau_J \leq T_i$;
- Let $T_i > 0$ time-to-event, $T_i = min(T_i^*, C_i)$;
  - $C_i$ censoring time for the i*th* subject;
  - $v_i$ indicated the right censored data;
  - $T_i^*$ the exact survival time;
- $\mathbf{Z}_i$ denote covariates.

# Joint hierarchical dynamic models (hdc) with structural change model

## Longitudinal Part

$$
\begin{aligned}
Y_{ij} &= \mu_{ij} + e_j, \quad e_j \sim N(0, \tau), \\
\mu_{ij} &= \mu_1 + \theta S_{ij}, \quad \theta = \mu_2 - \mu_1, \quad \theta \in (0, +\infty)
\end{aligned} \tag{1a}
$$

The transition probability:

$$
\begin{aligned}
Pr[S_{ij} = 0 \mid S_{ij-1} = 0] &= q_j, \\
Pr[S_{ij} = 1 \mid S_{ij-1} = 1] &= p_j.
\end{aligned} \tag{2}
$$

the equation $\mu_{ij}$ can be rewrite $\mu_{ij} = \mu_1 \bar{S}_{ij} + \mu_2 S_{ij}$, onde $\mu_2 > \mu_1$

# Joint hierarchical dynamic models (hdc) with structural change model

## Survival Part

$$\text{Relative risk: } h_i(t) = h_{0i}(t)\exp\{F_1'\boldsymbol{\theta}\} \tag{3}$$

## Parametric approach

$$T \mid F_1(y_i^*) \sim \textit{Weibull}(r, \mu_i), \quad \mu_i = \exp\{\theta_0 + \theta_1 f(y_i^*) + \theta_2 arm_i, \},$$

$$\begin{aligned} \text{Baseline risk Weibull: } h_0(t_i) &= r t_i^{r-1} && (4)\\ \text{Baseline risk Gomperz: } h_0(t_i) &= \gamma_0 + \gamma_1 t_i, && (5) \end{aligned}$$

## Semi-parametric approach

$$\begin{aligned} h_k(t_i) &= \exp\{h_{0k}(t_i) + \theta_1 f(y_i^*) + \theta_2 arm_i, \} && (6)\\ h_{0,k} &= h_{0,k-1} + w_k, \quad \mathbf{w} \sim N[0, \boldsymbol{W}]. \end{aligned}$$

# Priors

Non-informative prior distribution are used.

# Specifics objectives II: Evaluated for the survival part

## the parameterization: $T \mid f(y_i^*)$

- M1: $T \mid \mu_i$
- M2: $T \mid \theta$

## The approach Parametric or semi parametric.

## The data set was generated as:

$T \mid \mu_i \sim Weibull(r, \mu_i)$, 20% right-censored.

Table: *A comparison models, where* $T \mid f(y^*)$ *defines the parameterizations* $M1 : T \mid \mu_i$ *or* $M2 : T \mid \theta$, *where DIC: Deviance information criterion and LPML: logarithm of the pseudo marginal likelihood.*

| Approach | $T \mid f(y^*)$ | DIC | LPML |
|---|---|---|---|
| Weibull | M1 | 6838,39 | -3285,06 |
| | M2 | 6806,32 | -3281,21 |
| Gompertz | M1 | 6856,88 | -3283,54 |
| | M2 | 6841,17 | -3283,21 |
| PHD | M1 | 7521,34 | -3281,55 |
| | M2 | 7442,54 | -3283,69 |

# Real case study

Childhood with episodes of diarrhoea data set collected by Federal University of Bahia, Bahia, in Serrinha, 170 km northwest of Salvador, capital of the state of Bahia, Brazil (from December/1990 and December/1991), available in Carvalho et.all (2012)

# Real case study

## Childhood with episodes of diarrhoea study

- Longitudinal study on $n = 860$ Childhood with diarrhea incidence.
- aged 6 to 48 months where assigned vitamin A or placebo every 4 months for 1 year.
- They were followed up at home three times a week and;
- With the standard definition of diarrhoea (3 liquid or semi-liquid stools in 24 h).

# Childhood with episodes of diarrhoea study

## Objective

- The study investigates the effect of vitamin A supplementation on diarrhoea;
- Joint model included structure change.

# Joint hierarchical dynamic models (hdc) with structural change model for Childhood with episodes of diarrhoea

Table: *A comparison of models*

| Abordagem | $T \mid f(y^*)$ | DIC | LPML |
|---|---|---|---|
| Weibull | M1 | 26464,02 | -12553,61 |
| | M2 | 13205,54 | -2976,92 |
| PHD | M1 | 13080,36 | -2976,66 |
| | M2 | 13096,53 | -2977,02 |

# Results

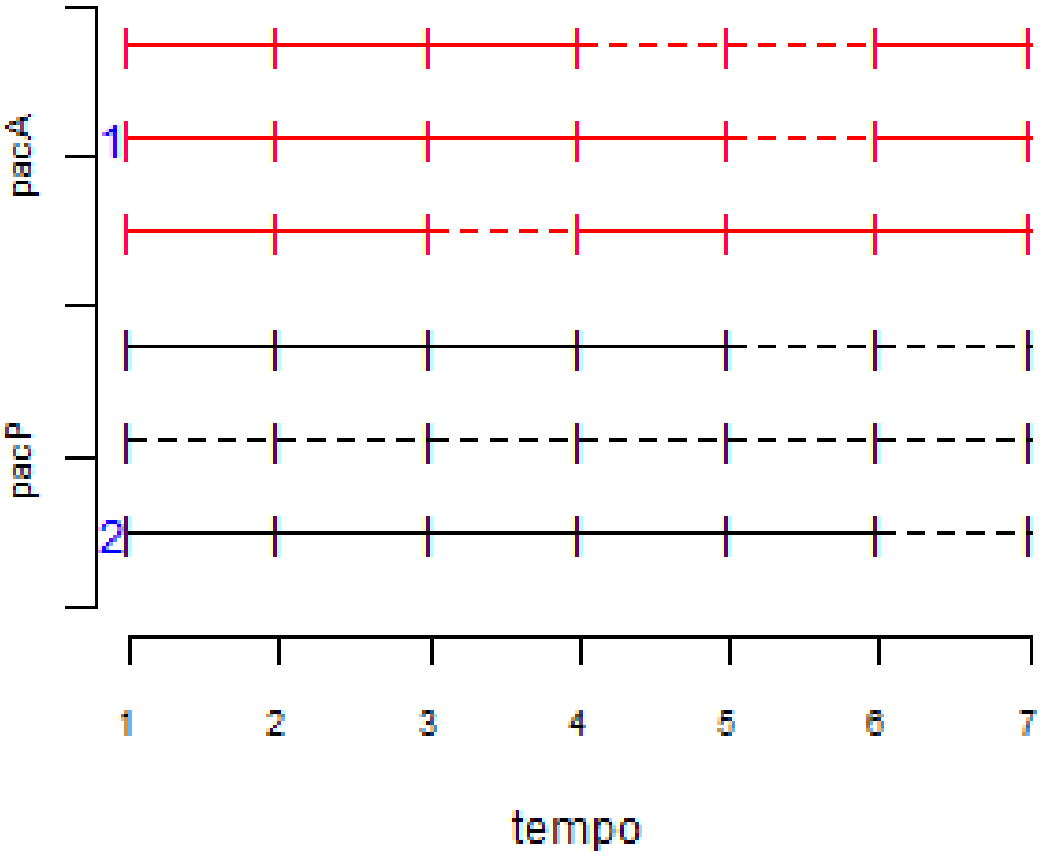
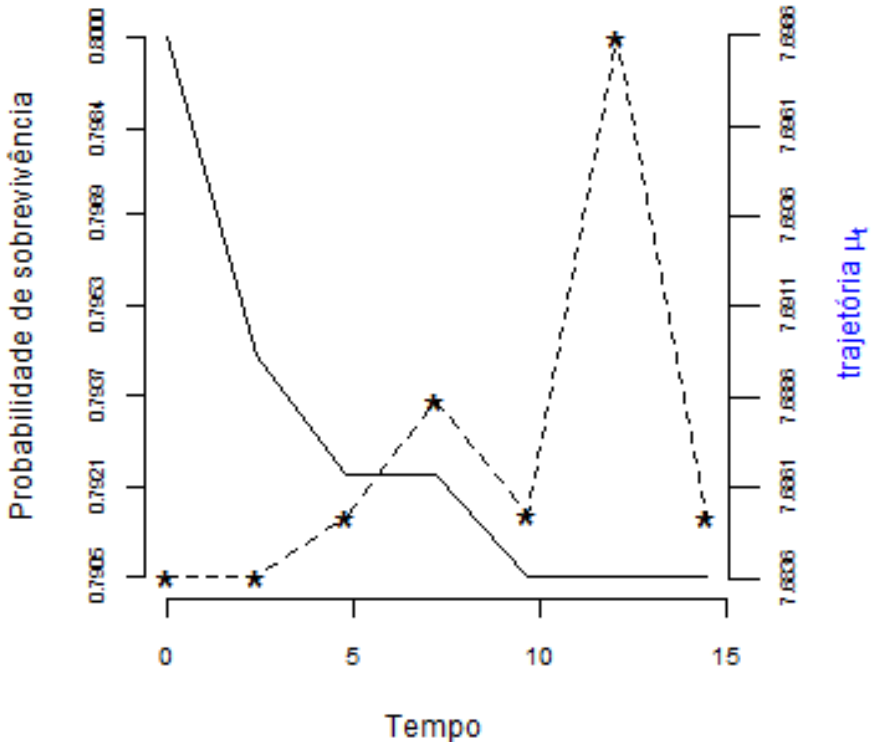



Figure: *Health status estimate for three patients according vit A (red), and plac (black) follow-up in days. The continuous line represent the regime 1 and dashed line regime 2.*

# Results

Patient Vit A




Patient Plac

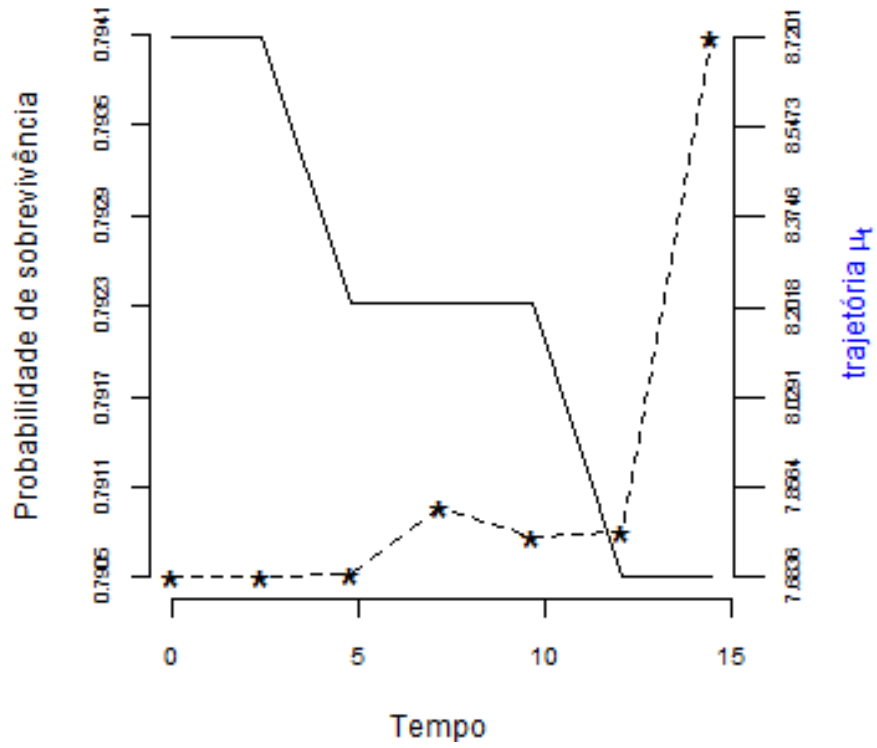



Figure: *Mean predictive posterior under longitudinal component and mean prediction survival function in simultaneous by treatments Vit, Plac .*

# Conclusions

- A new joint hierarchical dynamic model with structural change model is propose;
- The model incorporates health status non-progressive;
- The simulated study allows to evaluate the performance of parametrization $T \mid f(y_i^*)$.
- This application permits us to evaluate the longitudinal contribution in this study is 70% of *LPML*.

# Conclusions

- The posteriori distribution the health status transition probability and of health status progressive are sampled.
- Prediction survival including longitudinal predictions are present.

# Reference I


Brown, E. e Ibrahim, J. (2003) A bayesian semiparametric joint hierarchical joint models for longitudinal and survival data. *Biometrics*, **59**, 221–228.

Ghosh, S. e Mukhopadhyay, P. (2007) Bayesian analysis of quality adjusted lifetime (qal) data. *Journal of Statistical Theory and Practice*, **1**, 233–251.

Gou, X. e Carlin, B. (2004) Separate and joint modeling of longitudinal and event time data using standard computer packages. *The American Statistician*, **58**, 1–9.

Henderson, R., Diggle, P. e Dobson, A. (2000) Joint modelling of longitudinal measurements and event time data. *Biostatistics*, **1**, 465–480.

Kim, C. e Nelson, C. (1999) *State Space Models with Regime Switching*. The MIT Press.

Rizopoulos, D. (2012) *Joint Models for Longitudinal and Time to event data*. A Chapman & Hall.

# Reference II

Silva, G., Lima, A. e Sen, P. (2009) A semi markov multistate model for estimation of the mean quality adjusted survival for non progressive processes. *Lifetime Data Anal*, **15**, 216–240.

Wulfsohn, M. e Tsiatis, A. (1997) A joint model for survival and longitudinal data measured with error. *Biometrics*, **53**, 330–339.

Muchas Gracias! V Cobal , CIMAT

The Brazilian agencies grants: Capes, Cnpq, FapeRj