Random Change-Point Non-linear Mixed Effects Model for left-censored longitudinal data: An application to HIV surveillance

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Abstract

A change-point model is essential in longitudinal data to infer an individual specific time to an event that induces a change of trend. However, in general, change points are not known for population-based data. We present an unknown change-point model that fits the linear and non-linear mixed effects for pre- and post-change points. We address the left-censored observations. Through stochastic approximation expectation maximization (SAEM) with the Metropolis Hasting sampler, we fit a random change-point non-linear mixed effects model. We apply our method on the longitudinal viral load (VL) data reported to the HIV surveillance registry from New York City.

Key Words: Antiretroviral therapy, Censored data, Change-point, Longitudinal data, Metropolis–Hastings sampler, Mixed-effect model, Stochastic approximation, Expectation maximization

1. Introduction

Longitudinal nonlinear data are seen in many application fields. A change point that induces simultaneous trajectory changes and provides different trends for pre- and post-change points. These change-points differ for different subjects and are considered as random. In longitudinal data analysis, random change-point models have been widely used in medical research (Dominicus et al. 2008). The linear mixed effects models for pre- and post-random change points are a general way to define a class of random change point models (Rudoy et al. 2010, Moss et al. 2016, Buhule et al. 2020).

In a study of longitudinal data from HIV, an antiretroviral therapy (ART) is extremely effective and is the random change-point that separates two distinct trends of the HIV viral load (VL). The VL data in HIV is a widespread indicator of the evolution of HIV-infection (Perelson et al., 1996). Therefore, the effectiveness of antiviral treatment in HIV patients is measured by the reduction of viral loads (Ding and Wu 2000, 2001, 2002; Jacqmin-Gadda et al., 2000). As a biological process, we can assume that before ART, a viral load might be increasing in the HIV patient; and after ART, viral load may possibly be decreasing.

Typically, viral load shows a dramatic fluctuation after HIV infection before reaching a set-point and will then increase with a steady rate until the development of AIDS if there is no treatment (Mei et al., 2008). ART initiation, however, induces substantial reductions in HIV RNA. The viral load typically has a lower limit of quantification, and hence data include left-censored observations. The proportion of left-censored observations may not be small but could be more than one-third of the total observations. Hughes (1999) proposed a Monte-Carlo version of the expectation maximization (EM) algorithm (Dempster et al., 1977), taking into account

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the censored values as missing data. Jacqmin-Gadda et al. (2000) proposed a direct maximization of the likelihood using an iterative process for linear mixed models as well, including an autoregressive error model. Samson et al.(2006) used a truncated Gaussian distribution to impute censored observations. We use the right-truncated Gaussian distribution with the truncation limit as the linear function of the time.

The aim of this paper is to propose a random change-point model for left-censored longitudinal data and fit the linear mixed effect for pre-change-point, and a non-linear mixed effect model for post-change point through the stochastic approximation of the EM algorithm (SAEM) proposed by (Samson et al. 2006). We apply the random change-point model to the HIV longitudinal data.

In Section 2, we present a model for the random change-point non-linear model, Section 3 presents the SAEM algorithm and computation. In Section 4 we apply this methodology to HIV surveillance data. The conclusion is in Section 5.

2. Model

2.1 Notation and Model

Let us consider longitudinal sample data from n subjects with an explanatory time variable $\boldsymbol{t}$ and a response variable $\boldsymbol{y}$. The i^{th} subject has n_i observations. The j^{th} observation for the i^{th} subject at time t_{ij} has response value y_{ij}; $i = 1, \cdots, n$; $j = 1, \cdots, n_i$. The response values are either recorded with true observed values or left-censored threshold values ($Thres$). We denote observed or left-censored responses as:

$$y_{ij} = \begin{cases} y_{ij,obs} & \text{if} y_{ij} > \ Thres, \ y_{ij} \in I_{obs} \\ y_{ij,cen} & \text{if} y_{ij} \leq Thres, \ y_{ij} \in I_{cen}. \end{cases}$$

The response vector is $\boldsymbol{y_i} = (y_{i1,obs}, y_{i2,obs}, \cdots, y_{in_i,cen})'$ for the the i^{th} subject having left-censored observations.

We assume the random change-point non-linear mixed effect function with a linear trend before the change-point and a non-linear trend after change-point as follows

$$y_{ij} = e^{\alpha_{1i}}(t_{ij} - e^{\tau_i})^- + log_{10}(e^{\beta_{1i}} e^{-e^{\beta_{2i}}(t_{ij} - e^{\tau_i})^+} + e^{\beta_{3i}} e^{-e^{\beta_{4i}}(t_{ij} - e^{\tau_i})^+}), \qquad (1)$$

where $c(.)^- = \min(c(.), 0)$; $c(.)^+ = \max(c(.), 0)$. This function has six subject-level parameters including a random change-point τ_i. The linear parameter α_{1i} describes the linear trend before the change-point. The nonlinear parameters, β_{1i} and β_{3i} are baseline values, and β_{2i} and β_{4i} are two phase decay rates. We expontiate each of these parameters as the function coefficients take positive values to meet a biological property. The linear trend of the response describes the linear property of the response before the change-point and the nonlinear trend of the response describes the sudden decrease in responses after a change-point. The nonlinear segment in the above function is a bi-exponential model. The bi-exponential model for initial HIV was proposed by Ding and Wu (2001).

For simplicity, we write only $f(\boldsymbol{\phi}_i, t_{ij})$ or write as the sum of two pieces, the linear function $g(.)$ and the non-linear function $h(.)$ segmented by the random change-point τ_i

$$y_{ij} = f(\phi_i, t_{ij}) = g((t_{ij} - \tau_i)^-, \boldsymbol{\alpha}) + h((t_{ij} - \tau_i)^+, \boldsymbol{\beta}) \qquad (2)$$

where, $\boldsymbol{\alpha}$ is the linear mixed effects parameter, and $\boldsymbol{\beta}$ is the non-linear mixed effects parameter. We assume that mixed effects are a linear combination of fixed effects

and random effects. That is

$$\alpha_{1i} = \alpha_1 + a_{1i}, \beta_{1i} = \beta_1 + b_{1i}, \beta_{2i} = \beta_2 + b_{2i}, \beta_{3i} = \beta_3 + b_{3i}, \beta_{4i} = \beta_4 + b_{4i}, \tau_i = \tau + \tau_{1i},$$

with fixed-effect parameters $\boldsymbol{\mu} = (\alpha_1, \beta_1, \beta_2, \beta_3, \beta_4, \tau)'$ and subject-specific random effect parameters $\boldsymbol{P_i} = (a_{1i}, b_{1i}, b_{2i}, b_{3i}, b_{4i}, \tau_{1i})'$.

A random change-point non-linear mixed effect model is

$$\begin{aligned} y_{ij} &= g((t_{ij} - \tau_i)^-, \boldsymbol{\alpha}) + h((t_{ij} - \tau_i)^+, \boldsymbol{\beta}) + e_{ij}, \\ \boldsymbol{\phi}_i &= \boldsymbol{\mu} + \boldsymbol{P_i}, \\ \boldsymbol{P_i} &\sim ,\mathcal{N}(\mathbf{0}, \Omega), \\ e_{ij} &\sim \mathcal{N}(0, \sigma^2), \\ \tau_i &\sim \mathcal{N}(0, \sigma_\tau^2), \end{aligned} \tag{3}$$

We consider $\boldsymbol{\phi}_i$ where $i = 1, \cdots, n$ as missing data in modeling. The complete population parameter set is $\boldsymbol{\theta} = (\boldsymbol{\mu}, \Omega, \sigma^2, \sigma_\tau^2)$. With censored and missing data the complete likelihood is

$$f(\boldsymbol{y}, \boldsymbol{\phi}; \boldsymbol{\theta}) = \prod_{i=1}^{n} \prod_{j \in I_{obs}} f(y_{ij,obs}; \boldsymbol{\phi}_i, \boldsymbol{\theta})\, \pi(\boldsymbol{\phi}_i; \boldsymbol{\theta}) \prod_{i=1}^{n} \prod_{j \in I_{cen}} f(y_{ij,cen}; \boldsymbol{\phi}_i, \boldsymbol{\theta})\, \pi(\boldsymbol{\phi}_i; \boldsymbol{\theta}) \tag{4}$$

We assume that responses have an independent normal distribution with mean $g((t_{ij} - \tau_i)^-, \boldsymbol{\alpha}) + h((t_{ij} - \tau_i)^+, \boldsymbol{\beta})$, and constant variance σ^2. The complete loglikelihood is then

$$\begin{aligned} log(f(\boldsymbol{y}, \boldsymbol{\phi}; \boldsymbol{\theta})) = &-(\sum_{i=1}^{n} \sum_{j \in I_{obs}} n_i) log(\sigma^2) - \frac{1}{2\sigma^2} \sum_{i=1}^{n} \sum_{j \in I_{obs}} (y_{ij,obs} - (g(.) + h(.)))^2 \\ &-(\sum_{i=1}^{n} \sum_{j \in I_{cen}} n_i) log(\sigma^2) - \frac{1}{2\sigma^2} \sum_{i=1}^{n} \sum_{j \in I_{cen}} (y_{ij,cen} - (g(.) + h(.)))^2 \\ &-\frac{n}{2} log|\Omega| - \frac{1}{2} \sum_{i=1}^{n} (\boldsymbol{\phi}_i - \boldsymbol{\mu})' \Omega^{-1} (\boldsymbol{\phi}_i - \boldsymbol{\mu}) \\ &-\frac{n}{2} log(\sigma_\tau^2) - \frac{1}{2\sigma_\tau^2} \sum_{i=1}^{n} (\tau_i - \tau)^2. \end{aligned} \tag{5}$$

3. The estimation procedure

3.1 Starting values

The starting values of the random change-point are obtained Log 1-plus rule (Braunstein SL et al., 2016). Once we have the initial random change-point for each subject, we separate pre- and post-change-point observations. With each pre-change-point we fit a linear mixed effects model, and with each post-change-point we fit a nonlinear mixed effects model to approximate the initial parameters.

3.2 Estimating left-censored data

We use a truncated normal distribution to draw censored data. The censored data are recorded with the quantifying limit value of the experiment. So, we use the same censored limit as the upper truncation limit for all censored observation, $j \in I_{cen}$.

The lower limit of the censored data should be time dependent, and it is assumed that the lower limit decreases with time.

We assume the lower limit of truncation has a decreasing trend with respect to time t_{ij}. To facilitate, we find a simple linear regression coefficient for $y_{ij,cen,k-1}$ and $t_{ij,k-1}$ at the k^{th} iteration, $(i,j) \in I_{cen}$, where $y_{ij,cen,k-1}$ is the estimated censored observation $y_{ij,cen}$ at the $(k-1)^{th}$ iteration. With the assumption of a negative regression coefficient we obtain a restricted regression coefficient β_k^{cen}. We use this coefficient to update the right limit of the restricted distribution as $y_{ij,cen,k-1} + t_{ij}\beta_k^{cen}$.

3.3 The SAEM algorithm

The classical approach for an expectation maximization (EM) algorithm was introduced by Dampster et al. (1977), which estimates the model parameters for an incomplete data set. A brief note on an EM algorithm: an EM algorithm has an expectation step and a maximization step. Let $L(\boldsymbol{y}, \boldsymbol{\phi}; \boldsymbol{\theta})$ be the loglikelihood function of the complete data set. Define a function $Q(\boldsymbol{\theta}|\boldsymbol{\theta'}) = E(L(\boldsymbol{y}, \boldsymbol{\phi}; \boldsymbol{\theta})|\boldsymbol{y}; \boldsymbol{\theta'})$. The EM algorithm is the sequence of iterative estimation, at the k^{th} iteration; the E step is the evaluation of $Q_k(\boldsymbol{\theta}) = Q(\boldsymbol{\theta}|\boldsymbol{\theta}_k)$ and the M step updates $\hat{\boldsymbol{\theta}}_k$ by maximizing $Q_k(\boldsymbol{\theta})$. This mixed effect problem considers individual random effects $\boldsymbol{\phi}_i, i = 1, \cdots, n$ as missing data,and it makes our data an incomplete data set. The observed data and missing data together make up a complete data set. We use the stochastic approximation expectation maximization (SAEM) algorithm introduced by Delyon et al. (1999), which converges, under general conditions for the exponential family. For the exponential family the loglikelihood is

$$log(f(\boldsymbol{y}, \boldsymbol{\phi}; \boldsymbol{\theta})) = -\Lambda(\boldsymbol{\theta}) + < S(\boldsymbol{y}, \boldsymbol{\phi}), \boldsymbol{\Phi(\theta)} >$$

where, $\Lambda(.)$ and $\Phi(.)$ are functions of parameter $\boldsymbol{\theta}$, $S(\boldsymbol{y}, \boldsymbol{\phi})$ minimal sufficient statistics of the complete model, and $< ., . >$ is the scalar product. In the SAEM algorithm the E-step has two steps: simulation step (S-step) and Stochastic Approximation (SA) step, then the M-step for Maximization. In the simulation step (S step) the missing data $\boldsymbol{\phi}_i, i = 1, \cdots, n$ are sampled from its conditional distribution $\boldsymbol{\phi}_i|\boldsymbol{y}; \boldsymbol{\theta}$. The SA step uses the decreasing positive sequence of positive numbers decreasing toward zero $(\gamma_k)_{k \geq 0}$ for $E[S(\boldsymbol{y}, \boldsymbol{\phi})|\hat{\boldsymbol{\theta}}_k]$ with

$$s_{k+1} = s_k + \gamma_k(S(\boldsymbol{y}, \boldsymbol{\phi}) - s_m).$$

The sufficient statistics are $S^{(1)} = \sum_{i=1}^{n} \boldsymbol{\phi}_i$, $S^{(2)} = \sum_{i=1}^{n} \boldsymbol{\phi}_i^2$ and $S^{(3)} = \sum_{i=1}^{n} \sum_{j=1}^{n_i} [\boldsymbol{y_i} - f(\boldsymbol{\phi}_i, t_{ij})]^2$. In the M step the fixed effects are updated by maximizing the loglikelihood function which reduces to

$$\begin{aligned}
\hat{\boldsymbol{\mu}}_k &= \frac{1}{n} s_k^{(1)} \\
\hat{\omega}_k &= \frac{1}{n}(s_k^{(2)} - (s_k^{(1)})^2) \\
\hat{\sigma}_k &= \frac{1}{\sum_{i=1}^{n} n_i} s_k^{(3)}
\end{aligned}$$

3.4 Sampling and Computation

There is no closed-form analysis for this random change-point non-linear mixed effect model. We use the Metropolis–Hastings algorithm, the Markov chain Monte

Carlo (MCMC) method to obtain a sequence of random samples where there is no analytic solution. In the S step, we estimate the subject specific random effect $\boldsymbol{\phi}_i$ and the left-censored data $\boldsymbol{y_{ij,cen}}$. The Gibbs sampling to estimate these two sets of vectors at the k^{th} iteration is as follows:

1. Sample random effects using the Metropolis-Hastings (MH) algorithm with a target distribution as a conditional distribution $p(.|\boldsymbol{y}; \hat{\boldsymbol{\theta}}_{k-1})$

2. Simulate the censored observation with a right-truncated normal distribution.

In the MH-algorithm, the proposal distribution is the multivariate normal distribution $\mathcal{N}(\boldsymbol{\mu}_{k-1}, \hat{\Omega}_{k-1})$. Kuhn and Lavielle presented the details of the SAEM implementation and proved that under a general hypothesis, the sequence $(\hat{\boldsymbol{\theta}}_k)_{k\geq 0}$ obtained by this algorithm converges almost surely toward a (local) maximum of the likelihood $L(\boldsymbol{y}; .)$.

We simulated the k^{th} censored observation $y_{ij,cen}$ from the right-truncated normal distribution $\mathcal{N}(f(\boldsymbol{\phi}_{i,k}, t_{ij}), \sigma_k^2)$. The upper limit of the truncation distribution is as defined in Subsection 3.2.

4. Application

We apply the model to HIV data with left-censored observations. The data source is HIV surveillance registry data from the New York City (NYC) Department of Health and Mental Hygiene (DOHMH) for years 2006 to 2015, for patients with age 13 years or above. The electronic reporting to the NYC DOHMH of all HIV-related laboratory tests conducted in NYC have data that includes positive diagnostic tests, viral load (VL) data and time of visit. In this application, we have data from 500 subjects with average of 5.0 visits per subject which make about 2500 total observations. The data include left-censored observations. About 40% of the observation are left-censored. The limit of quantification of VL are 200 cp/ml., 100 cp/ml or 50 cp/ml. For a computational purposes, the original time unit (days) is rescaled by (5* 365).

Table 1 shows the estimated population parameters ($\boldsymbol{\theta}$) for the HIV registry data. The population random change-point parameter τ, ART initiation time, is estimated at -2.49 with a 95% confidence interval of (0.-5.89, 0.897), ($e^{-2.49} = 0.082$, makes 151.3 days). The error $\hat{\sigma_\tau^2} = 2.99$. The pre-ART viral load has a linear slope parameter estimated at $\hat{\alpha} = -1.98$. The estimated random error term $\hat{\sigma^2} = 0.536$. Figure 1 shows the convergence of the random change-point model for a typical simulation.

5. Conclusion

This research works on longitudinal data with random change points having left-censored data. It extends the non-linear mixed effect model to the random change point non-linear mixed effect model, where change point discriminate between linear and non-linear models for pre- and post-change-points. We fit a model within a Stochastic approximation expectation maximization (SAEM) algorithm framework, which uses the Metropolis-Hastings sampler. We have accommodated left-censored observations to address the general possible censored observations in biomedical field. The left-censored observations are sampled through a right-truncated normal

Table 1: Parameters estimated for HIV surveillance data from New York City for 2006-2015

Estimation of fixed effects						
Parameters	α_1	β_1	β_2	β_3	β_4	τ
Estimate	-1.985	3.411	0.460	10.941	5.680	-2.497
Standard Error	1.004	0.129	0.380	0.145	0.082	0.191
95% CI (lower)	-3.953	3.158	-0.284	10.658	5.520	-2.871
95% CI (upper)	-0.017	3.665	1.204	11.224	5.840	-2.123
Estimation of the variance component						
Parameters	$\sigma^2_{\alpha_1}$	$\sigma^2_{\beta_1}$	$\sigma^2_{\beta_2}$	$\sigma^2_{\beta_3}$	$\sigma^2_{\beta_4}$	σ^2_{τ}
Estimate	0.027	0.127	0.324	1.304	0.103	2.998
Standard Error	3.660	0.090	0.539	0.234	0.048	0.371

distribution with a lower limit of restriction dependent upon the time variable. The initial change-points are approximated through an exponential curve fitting.

We have applied this method to the HIV surveillance registry data from the New York City (NYC) Department of Health and Mental Hygiene (DOHMH) for years 2006 to 2015, for patients with ages 13 years or above. The population random change-point parameter τ is estimated at 151 days and random error $\sigma^2_\tau = 2.99$.

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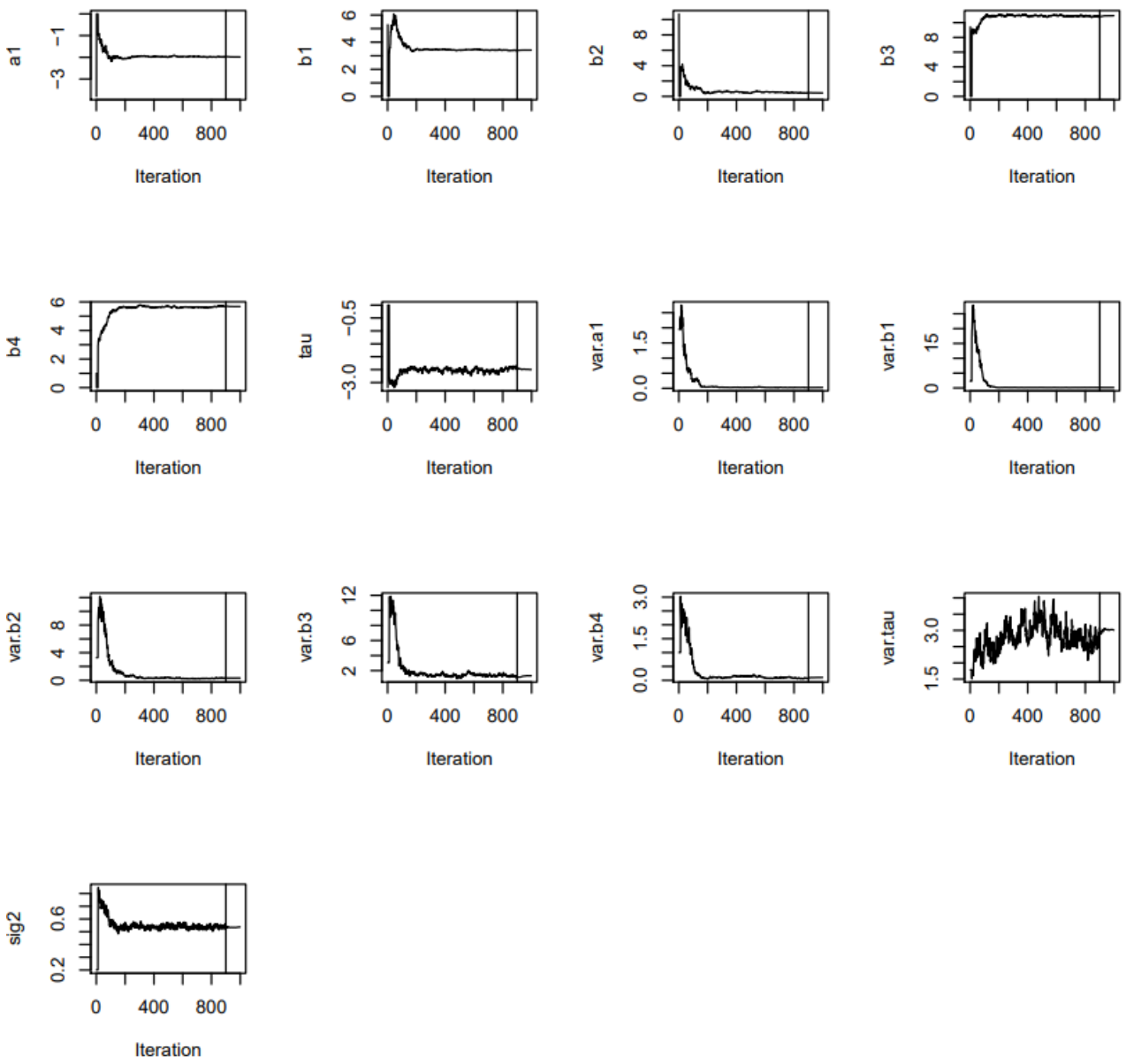

Figure 1: Convergence plot of random change-point parameters (application to HIV, in simulation)