Beta-binomial mixed models: Application in longitudinal health related quality of life data

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September 8, 2016

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Motivation

Health related quality of life:

- Increasingly important indicator of health status.
- Information about the disease and its impact in the patient in a standardized, comparable and objective way.
- Short-Form 36 Health Survey.

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Health related quality of life:

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- Short-Form 36 Health Survey.

Goal: Study the relationship of HRQoL with patients and diseases characteristics.

Short-Form 36 Health Survey

- It has 36 items, with different answer options.
- It provides a way to measure HRQoL from the patient's point of view.
- Represents eight of the most important health dimensions:

1. Physical functioning
2. Role-physical
3. Bodily pain
4. General health
5. Vitality
6. Social functioning
7. Role-emotional
8. Mental health

Longitudinal study

- Carried out in Galdakao Hospital (Viscay).
- Goal: measure the health status and evolution of patients being treated for COPD.
- Patients were followed for up to five years.
- 543 patients and 4 measurements.

Longitudinal study

- The 10% of the population in European Union suffers this disease.
- It is characterized by time to time deterioration.
- It is the fourth cause of death due to disease in the world.
- There is a large variability in the medical decision procccess, including hospitalization criterion.

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Literature

Beta-binomial distribution for analysing HRQoL (Arostegui et al., 2007).

Beta-binomial regression:

- "logistic" regression (Forcina and Franconi 1988).
- Hierarchical GLM (Lee and Nelder 1996).

Literature

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"logistic" regression is more adequate in HRQoL data (Najera-Zuloaga et al., 2016).

Problem/Theoretical motivation

Beta-binomial distribution:

- Consists of a sum of correlated Bernoulli variables.

$$y \sim \text{BB}(m, p, \phi) \Leftrightarrow y|u \sim \text{Bin}(m, u), \;\; u \sim \text{Beta}(p/\phi, (1-p)/\phi)$$

$$\text{E}[y] = mp, \qquad \text{Var}[y] = mp(1-p)[1 + (n-1)\frac{\phi}{1+\phi}]$$

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Problem:

- Beta-binomial does not belong to exponential family.
- No mixed model developed:

$$\eta = \text{logit}(p/(1-p)) = X\beta + Zu$$

Definition

Given some outcome variables $y_1, y_2, \ldots, y_n$, we have that

$$y_i|u \sim \text{BB}(m, p_i, \phi) \qquad \text{and} \qquad u \sim \mathcal{N}(0, D).$$

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Given the covariates $X_1, X_2, \ldots, X_p$, we construct the following linear predictor:

$$\eta_i = \text{logit}(p_i) = x_i'\beta + z_i'u$$

where x_i and z_i are the ith row of full rank matrices X and Z, consisting of the given covariates and the random structure of the model.

Estimation process

It is focused on the following approximated likelihood

$$l(\beta, \theta | y, \tilde{u}) = -\frac{1}{2}\log(\det(D^*)) + h(\tilde{u})$$

where,

h is the hierarchical likelihood defined by Lee and Nelder (1996),

$\tilde{u}$ is the solution of $\frac{\partial h}{\partial u} = 0$,

and, $D^* = \frac{\partial^2 h}{\partial u \partial u'}|_{u=\tilde{u}}$.

Creating the data

Simulated longitudinal scenario:

- n^o of individuals 50, n^o of time measurements 3.
- $x \sim \mathcal{N}(1, 1)$.
- $\beta_0 = -1, \beta_1 = 2$.
- $u \sim \mathcal{N}(0, \sigma^2 I_3)$, where $\sigma = 2$.
- $\eta_i = x_i'\beta + z_i'u \Longrightarrow p_i = 1/(1 + exp(-\eta_i))$.
- $\phi = 2$ and $m = 10$.
- $y_i \sim \text{BB}(m, p_i, \phi)$.

The toy data

ID	$t = 1$	$t = 2$	$t = 3$
1	10	10	10
2	10	2	NA
3	10	NA	NA
⋮	⋮	⋮	⋮
50	1	10	NA
	$n_1 = 50$	$n_2 = 45$	$n_3 = 26$

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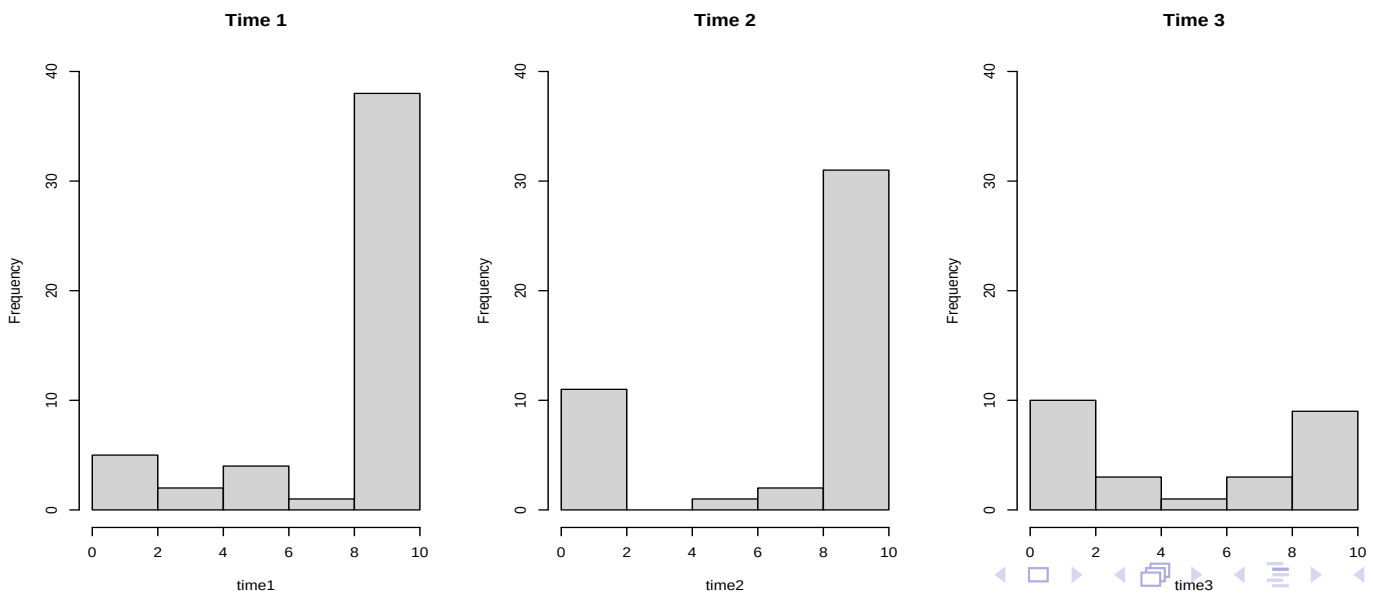
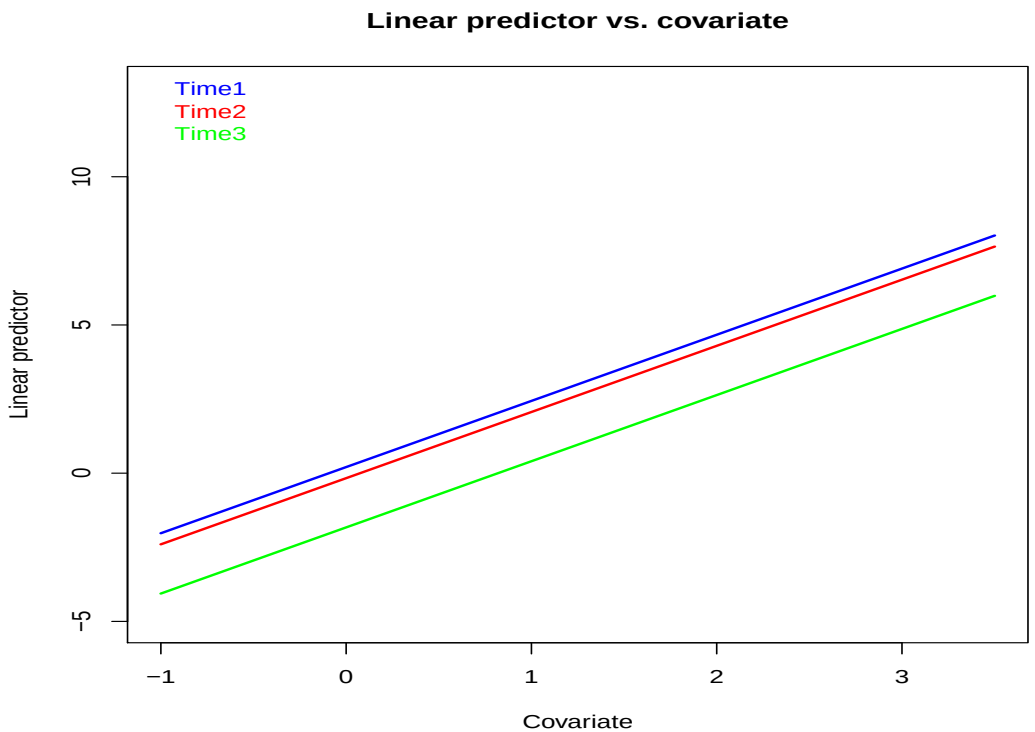


Different models

$$\boxed{\Delta x \rightarrow \Delta y_t}$$

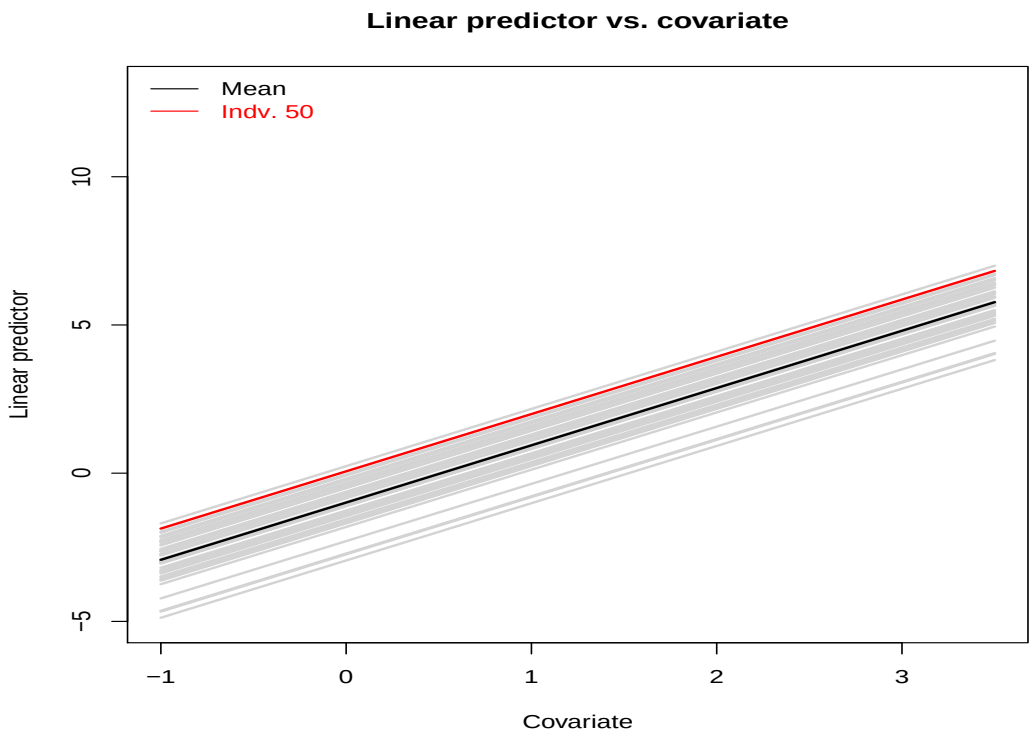
Random intercept per time: $\eta_{it} = \beta_0 + x_{it}\beta_1 + u_t$



Different models

$$\boxed{\Delta x \rightarrow \Delta y_i}$$

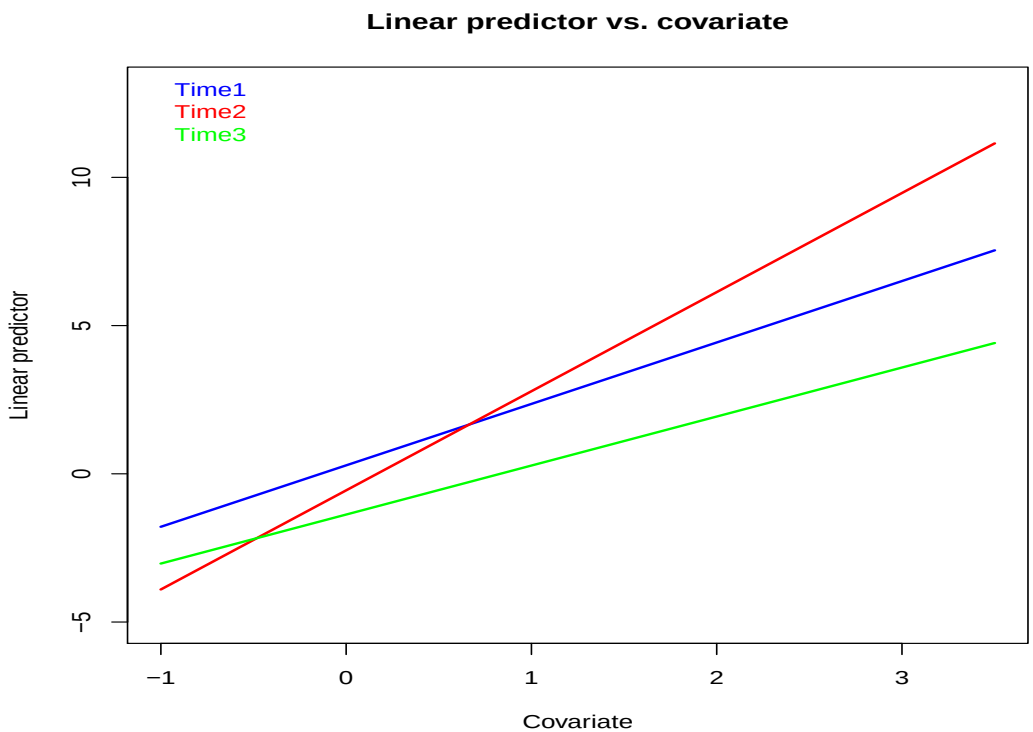
Random intercept per individual: $\eta_{it} = \beta_0 + x_{it}\beta_1 + v_i$



Different models

$$\boxed{\Delta x \rightarrow \Delta y_t}$$

Random intercept and slope: $\eta_{it} = \beta_0 + x_{it}(\beta_1 + \beta_t) + u_i + v_t$



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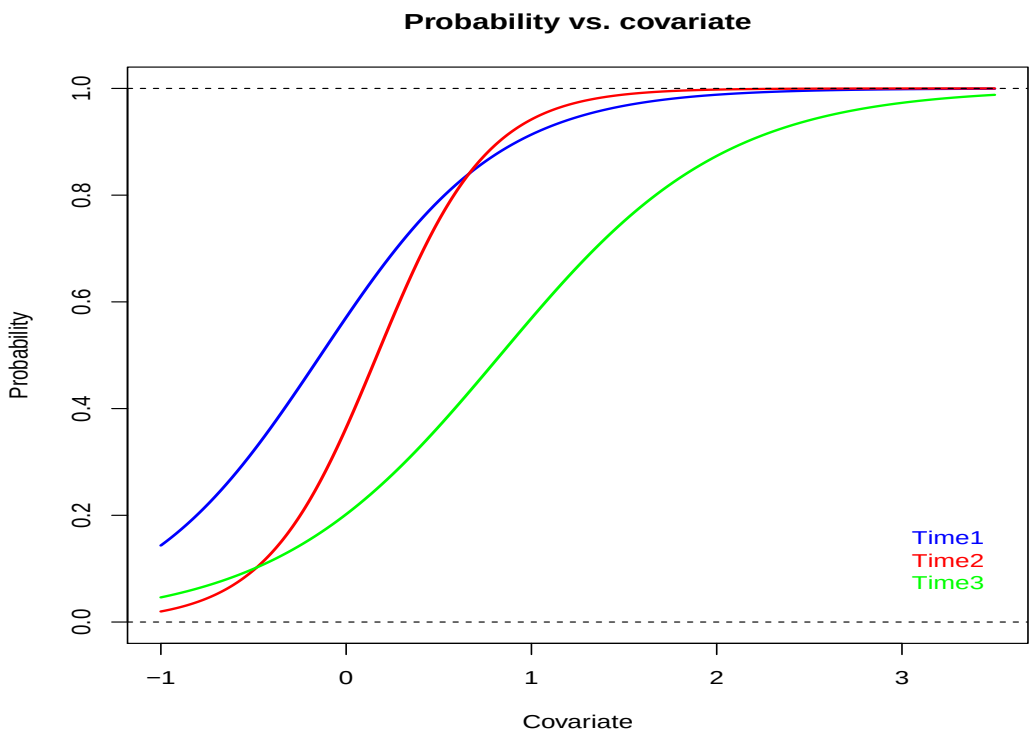


Package example

`R`-package: `HRQoL`

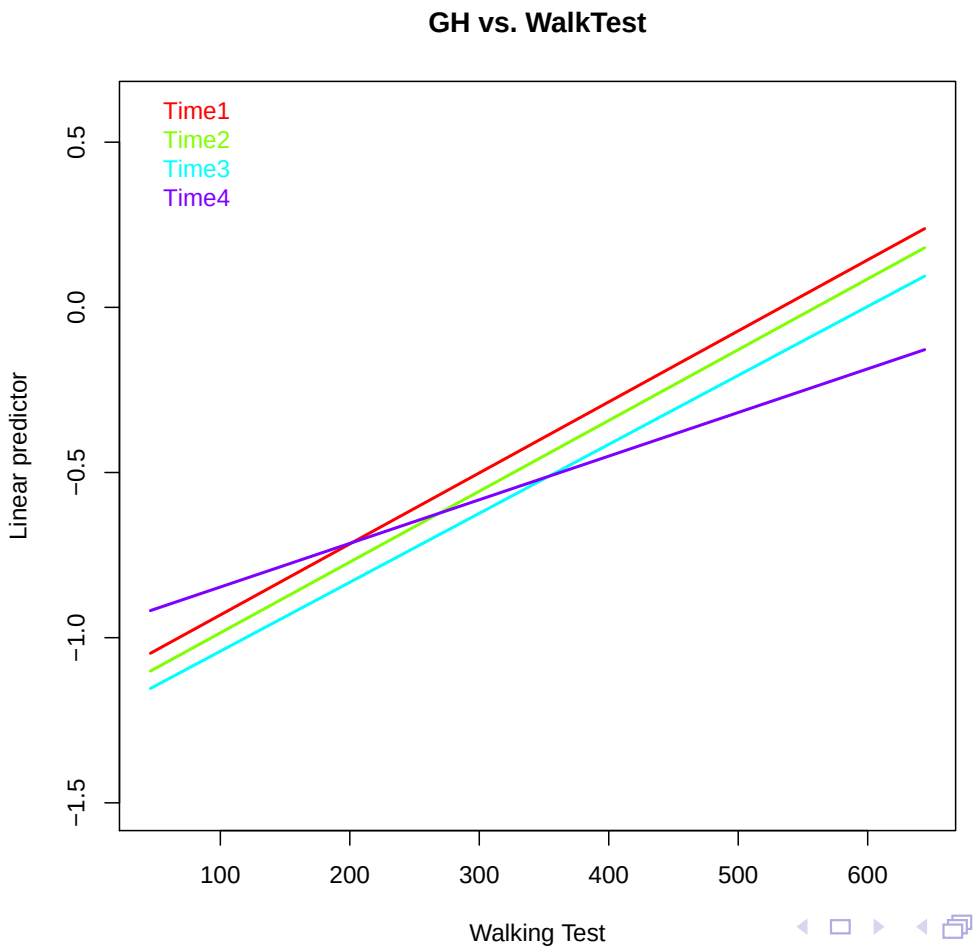
- HRQoL plots.
- Recodes.
- Beta-binomial distribution based analysis.
- Longitudinal models.
- ....

R-package: HRQoL

```
Call: BBmm(fixed.formula = y~x, random.formula=~ID+time, m, data)

Fixed effects coefficients:

            Estimate   StdErr t.value   p.value
(Intercept) 1.001291 0.096883  10.335 < 2.2e-16 ***
x           2.005359 0.101176  19.820 < 2.2e-16 ***
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
-------------------------------------------------------------

Random effects standard error coefficients:

     Estimate StdError t.value  p.value
[1,]  0.95878  0.26539  3.6127 0.000303 ***
[2,]  1.01272  0.31701  3.1946 0.001400 **
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Number of random components in each random effect: 11 6
-------------------------------------------------------------

Beta-binomial transformed dispersion parameter coefficients:

    Estimate StdError t.value   p.value
psi -1.06365  0.11366 -9.3579 < 2.2e-16 ***
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
-------------------------------------------------------------

Number of observations: 1000

Number of iterations: 5
```

Real application: General health dimension

$$\eta_{it} = \beta_0 + (\beta_1 + \beta_t)\text{WalkingTest}_{ij} + u_i + v_t$$



Future work

- Structure of the random effects: Temporal correlation.
- Different variances.
- Multidimensional framework: All dimensions together.

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