

A Joint Marginalized Multilevel Model for Longitudinal Outcomes

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1 Introduction

2 Methodology

- Models for single responses
- Models for joint responses

3 Estimation

4 Analysis of Case Study

- Data Description
- Analysis and Results: HCV and HIV data
- Analysis and Results: ARMD Trial

5 Concluding Remarks

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- **Separate analysis per outcome inadequate**

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- How treatment improves outcomes simultaneously
- **Associations between outcomes and their evolution**

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Advantages

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Models and Interpretations

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Models and Interpretations

- Shared parameter model
- Random effect extensions

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- Shared parameter model
- Random effect extensions
- Marginal vs hierarchical
- Gaussian vs non-Gaussian

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Models for single responses

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- **Alternatively GEE, Marginalized multilevel models (MMM)**

Shared-parameter model / random effect extension

- Suppose Y_{1ij} and Y_{2ik} , $j = 1, 2, \dots, n_{1i}$, and $k = 1, 2, \dots, n_{2i}$

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- For a continuous and binary response

$$Y_{1ij} = \mathbf{x}'_{1ij}\boldsymbol{\beta} + \mathbf{z}'_{1ij}\mathbf{b}_i + \varepsilon_{ij}.$$

$$\eta(\mu_{ik}) = \eta[E(Y_{2ik}|\mathbf{b}_i)] = \mathbf{x}'_{2ik}\boldsymbol{\alpha} + \Lambda\mathbf{z}'_{2ik}\mathbf{b}_i.$$

where Λ is a re-scale parameter, $\mathbf{b}_i \sim N(0, \mathbf{D})$, $\varepsilon_{ij} \sim N(0, \mathbf{R}_i)$

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- Allow different random effects. Example,

$$\mathbf{b}_i = (b_{1i}, b_{2i})' \sim N \left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} d_{11} & d_{12} \\ d_{12} & d_{22} \end{pmatrix} \right]$$

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- Joint marginal distribution by integrating out random effects

Joint marginalized multilevel model

- Suppose Y_{1ij} and Y_{2ik} , $j = 1, 2, \dots, n_{1i}$ are binary outcomes

$$\eta(\mu_{1ij}^m) = \mathbf{x}'_{1ij} \boldsymbol{\beta}^m, \quad \eta(\mu_{2ij}^c) = \delta_{1ij} + \mathbf{z}'_{1ij} \mathbf{b}_{1i}$$

$$\eta(\mu_{2ik}^m) = \mathbf{x}'_{2ik} \boldsymbol{\alpha}^m, \quad \eta(\mu_{2ik}^c) = \delta_{2ik} + \mathbf{z}'_{2ik} \mathbf{b}_{2i}$$

where $\mathbf{b}_i \sim N(0, \mathbf{D})$, $\mu_{ij}^m = E(Y_{ij})$ and $\mu_{ij}^c = E(Y_{ij} | \mathbf{b}_i)$

Joint marginalized multilevel model

- $E(Y_{ij}) = E[E(Y_{ij}|\mathbf{b}_i)]$ used to solve for δ_{ij}

Thus

$$\mu_{ij}^m = g(\mathbf{x}'_{ij}\boldsymbol{\alpha}^m) = \int_b g(\delta_{ij} + \mathbf{z}'_{ij}\mathbf{b}_i) dF_b$$

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- For logit-logit link:

$$\text{expit}(\mathbf{x}'_{ij}\boldsymbol{\alpha}^m) = \int_b \text{expit}(\delta_{ij} + \mathbf{z}'_{ij}\mathbf{b}_i) f(\mathbf{b}_i) d\mathbf{b}_i.$$

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- For logit-probit link:

$$\delta_{ij} = \sqrt{1 + \mathbf{z}'_{ij}\mathbf{D}\mathbf{z}_{ij}} \cdot \Phi^{-1}[\text{expit}(\mathbf{x}'_{ij}\boldsymbol{\alpha}^m)]$$

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Maximum likelihood

- Joint marginal likelihood:

$$L(\beta, \alpha^m, D) = \prod_{i=1}^N f_i(\mathbf{Y}_{1i} = \mathbf{y}_i, \mathbf{Y}_{2i} = 1).$$

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- Easy to implement in SAS NLMIXED

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$$L(\beta, \alpha^m, D) = \prod_{i=1}^N f_i(\mathbf{Y}_{1i} = \mathbf{y}_i, \mathbf{Y}_{2i} = 1).$$

- Easy to implement in SAS NL MIXED
- Other techniques: Pseudo-likelihood, Bayesian estimation etc.

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- Apply joint models

Age Related Macular Degeneration Trial (Buyse and Molenberghs 1998)

- Randomized, multi-center clinical trial
- ARMD associated with progressive lost of vision
- Patients' visual acuity measured at 4 follow-up visits

Age Related Macular Degeneration Trial (Buyse and Molenberghs 1998)

- Randomized, multi-center clinical trial
- ARMD associated with progressive lost of vision
- Patients' visual acuity measured at 4 follow-up visits
- Aim was to compare experimental interferon- α to placebo
- We consider change in visual acuity (continuous) and whether or not there is loss of vision (binary response)
- Apply joint model to study treatment effect and association between the responses

Models

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$$\text{logit}(\mu_{1ij}) = \alpha_0 + \alpha_j T_{ij}, \quad \text{logit}(\mu_{2ij}) = \beta_0 + \beta_j T_{ij}$$

where T_{ij} is a year indicator (Year 9 is reference year)

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- Conditional mean model:

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- Models fit assessed with AIC**

Results for HCV and HIV data

Table: *Separate models for HIV and HCV prevalence.*

Effect	Hierarchical models		Marginal models			
	GLMM		GEE		MMM	
	HCV	HIV	HCV	HIV	HCV	HIV
Int.	0.5921(0.1124)	-2.1293(0.1839)	0.5088(0.1487)	-2.1474(0.2278)	0.5586(0.1049)	-1.9018(0.1716)
Time 1	0.2226(0.0111)	0.0197(0.0156)	0.2268(0.0796)	0.1180(0.1429)	0.2074(0.0110)	0.0283(0.0148)
Time 2	0.2091(0.0111)	-0.0283(0.0159)	0.2132(0.0685)	0.0519(0.1536)	0.1976(0.0110)	-0.0110(0.0151)
Time 3	0.2878(0.0111)	0.0432(0.0159)	0.2864(0.0629)	0.1064(0.1372)	0.2748(0.0114)	0.0417(0.0151)
Time 4	0.1792(0.0109)	-0.0035(0.0159)	0.1800(0.0574)	0.0507(0.1179)	0.1694(0.0107)	0.0021(0.0150)
Time 5	0.1060(0.0108)	-0.0081(0.0160)	0.1143(0.0531)	0.0410(0.1407)	0.1013(0.0104)	-0.0078(0.0151)
Time 6	0.1138(0.0107)	-0.0423(0.0161)	0.1199(0.0521)	-0.0006(0.1270)	0.1091(0.0103)	-0.0402(0.0153)
Time 7	0.0722(0.0107)	-0.0443(0.0163)	0.0692(0.0545)	-0.0268(0.1072)	0.0704(0.0102)	-0.0433(0.0155)
Time 8	-0.0369(0.0108)	-0.0776(0.0164)	-0.0276(0.0314)	-0.0494(0.0885)	-0.0350(0.0103)	-0.0742(0.0158)
RE Var.	0.2514(0.0796)	0.6710(0.2149)			0.0902(0.0286)	0.1802(0.05743)
Corr.			0.8377	0.9066		
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- Due to high random-effect variance, GLMM and GEE for HIV are more apart
- GEE and MMM have similar estimates (higher precision in full likelihood MMM)

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Table: *Joint models of HIV and HCV prevalence in Italy.*

Effect	Joint hierarchical models				Joint marginalized multilevel model			
	Shared RE		Correlated RE		Shared RE		Correlated RE	
	HCV	HIV	HCV	HIV	HCV	HIV	HCV	HIV
Intercept	0.5033 (0.0902)	-1.9939 (0.1741)	0.5909 (0.1125)	-2.1249 (0.1823)	0.4839 (0.0895)	-1.8833 (0.1684)	0.5574 (0.1050)	-1.9008 (0.1708)
Time 1	0.2044 (0.0110)	0.0193 (0.0155)	0.2226 (0.0111)	0.0110 (0.0156)	0.1943 (0.0108)	0.0337 (0.0154)	0.2073 (0.0110)	0.0284 (0.0148)
Time 2	0.1909 (0.0110)	-0.0226 (0.0159)	0.2091 (0.0111)	-0.0283 (0.0159)	0.1831 (0.0108)	-0.0121 (0.0158)	0.1976 (0.0110)	-0.0199 (0.0151)
Time 3	0.2734 (0.0110)	0.0477 (0.0159)	0.2878 (0.0111)	0.0433 (0.0159)	0.2629 (0.0110)	0.0496 (0.0158)	0.2747 (0.0114)	0.0417 (0.0151)
Time 4	0.1669 (0.0108)	-0.0007 (0.0158)	0.1792 (0.0109)	-0.0034 (0.0159)	0.1592 (0.0105)	0.0077 (0.0157)	0.1693 (0.0107)	0.0022 (0.0150)
Time 5	0.1008 (0.0107)	-0.0069 (0.0159)	0.1060 (0.0108)	-0.0080 (0.0160)	0.0974 (0.0103)	-0.0042 (0.0158)	0.1013 (0.0104)	-0.0077 (0.0151)
Time 6	0.1086 (0.0107)	-0.0390 (0.0160)	0.1138 (0.0107)	-0.0422 (0.0161)	0.1048 (0.0103)	-0.0361 (0.0160)	0.1091 (0.0103)	-0.0401 (0.0153)
Time 7	0.0685 (0.0106)	-0.0417 (0.0163)	0.0722 (0.0107)	-0.0443 (0.0163)	0.0673 (0.0102)	-0.0406 (0.0162)	0.0704 (0.0102)	-0.0433 (0.0155)
Time 8	-0.0426 (0.0108)	-0.0750 (0.0164)	-0.0369 (0.0108)	-0.0776 (0.0164)	-0.0403 (0.0103)	-0.0737 (0.0164)	-0.0350 (0.0103)	-0.0743 (0.0158)
Scale	1.9338 (0.0176)				1.6222 (0.0137)			
RE Var.	0.1613 (0.0511)		0.2517 (0.0798)	0.6589 (0.2107)	0.0646 (0.0205)		0.0903 (0.0286)	0.1784 (0.0568)
Corr.			0.7868 (0.0862)				0.7906 (0.0846)	
-2//	17181		9954		17221		9967	

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- **Correlated version of joint models fit better in terms of AIC**

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- $E(Y_{1ij}) = \beta_{0j} + \beta_{1j}T_i$ and $\text{logit}(E(Y_{2ij})) = \alpha_{0j} + \alpha_{1j}T_i$
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- **Compound symmetry (exchangeable) variance or correlation structure used**

Results for ARMD Trial

Table: The Age Related Macular Degeneration Trial.

Effect	Continuous sequence				Binary sequence				
	Marg. Corr.	Sep. hier.	Joint hier.	Joint MMM	GEE	GLMM	MMM	Joint hier.	Joint MMM
Int. 4	-3.2353 (0.8074)	-3.2526 (1.2968)	-3.2675 (1.2964)	-3.2682 (1.2964)	1.0151 (0.2442)	1.7424 (0.4204)	0.9965 (0.2375)	2.0111 (0.4625)	1.0346 (0.2326)
Int. 12	-4.6207 (1.0707)	-4.6207 (1.2922)	-4.6207 (1.2922)	-4.6207 (1.2922)	0.9083 (0.2369)	1.5610 (0.4108)	0.9103 (0.2372)	1.8151 (0.4535)	0.9280 (0.2307)
Int. 24	-8.3678 (1.2634)	-8.3678 (1.2922)	-8.3678 (1.2922)	-8.3678 (1.2922)	1.1451 (0.2505)	1.9534 (0.4294)	1.1496 (0.2515)	2.2375 (0.4707)	1.1648 (0.2454)
Int. 52	-15.1609 (1.6414)	-15.1609 (1.2922)	-15.1609 (1.2922)	-15.1609 (1.2922)	1.6514 (0.2918)	2.7633 (0.4805)	1.6308 (0.2867)	3.1073 (0.5200)	1.6296 (0.2792)
Trt. 4	2.3323 (1.0551)	2.3356 (1.7609)	2.3864 (1.7602)	2.3858 (1.7603)	-0.4187 (0.3198)	-0.6724 (0.5395)	-0.3732 (0.3143)	-0.6879 (0.5922)	-0.3568 (0.3045)
Trt. 12	2.3391 (1.5220)	2.3391 (1.7551)	2.3391 (1.7551)	2.3391 (1.7551)	-0.5351 (0.3104)	-0.8769 (0.5305)	-0.5120 (0.3114)	-0.9260 (0.5851)	-0.4774 (0.3036)
Trt. 24	2.8338 (1.8422)	2.8338 (1.7551)	2.8338 (1.7551)	2.8338 (1.7551)	-0.5240 (0.3248)	-0.8392 (0.5442)	-0.5013 (0.3260)	-0.8757 (0.5956)	-0.4686 (0.3176)
Trt. 52	4.1221 (2.3078)	4.1221 (1.7551)	4.1221 (1.7551)	4.1221 (1.7551)	-0.4049 (0.3756)	-0.6077 (0.5922)	-0.3651 (0.3689)	-0.6214 (0.6376)	-0.3382 (0.3556)
Res. Var.	-	70.9225 (4.2076)	67.4893 (3.8163)	67.7113 (3.8292)	-	-	-	-	-
RE Var.	-	74.3544 (9.5060)	-	-	-	4.7951 (1.1643)	1.5858 (0.3712)	-	-
Inflation	-	-	-3.3122 (0.3379)	-5.8694 (0.5697)	-	-	-	-	-
-2//	5480.73	5168.5	-	-	-	773.4	773.4	-	-
Common parameters in joint models									
RE Var.			7.0905 (1.5485)	2.2515 (0.4695)					
-2//			5744.7	5744.6					

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- Simulation study conducted confirms these findings

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- Data Description
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- The joint MMM models enjoys population average interpretation
- Yields estimates close to other marginal models
- Increases precision compared to single-outcome analysis
- Simulation study also confirms, joint models reduce bias
- Easy to implement using SAS procedure NLMIXED

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