Thesis: Third meeting

Fitting Multiple Outcome models with INLA

Georgy Gomon

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Outline

Pain dataset

- Dataset given as example in Weiss [4].
  - Measurements on pain tolerance and pain rating on 63 children
  - 4 measurements per child
  - 2 outcomes: Pain tolerance & Pain rating
  - 3 covariates: Treatment, sex & ses (socio-economic status)

	id	ses	sex	treatment	pain_tolerance	pain_rating
2.1	2	74.70	female	distract	3.34	6
2.2	2	74.70	female	distract	3.19	5
2.3	2	74.70	female	distract	2.76	4
2.4	2	74.70	female	distract	3.01	6
3.1	3	81.50	female	none	2.48	7
3.2	3	81.50	female	none	2.30	2

Method 2: Joint Mixed Model

Joint Mixed Model

$$\begin{cases} y_i(t_{ij}) = \mathbf{v}_{yi}^{\mathsf{T}}(t_{ij})\beta_{\mathbf{y}} + \mathbf{z}_{yi}^{\mathsf{T}}(t_{ij})\mathbf{b}_{yi} + \epsilon_{yi}(t_{ij}) \\ x_i(t_{ij}) = \mathbf{v}_{xi}^{\mathsf{T}}(t_{ij})\beta_{\mathbf{x}} + \mathbf{z}_{xi}^{\mathsf{T}}(t_{ij})\mathbf{b}_{xi} + \epsilon_{xi}(t_{ij}) \end{cases}$$

with

$$\begin{bmatrix} \mathbf{b}_{yi} \\ \mathbf{b}_{xi} \end{bmatrix} \sim \mathcal{N}(\mathbf{0}, \mathbf{D}); \quad \begin{bmatrix} \epsilon_{yi} \\ \epsilon_{xi} \end{bmatrix} \sim \mathcal{N}_{n_i}(\mathbf{0}, \Sigma_i)$$

$$\epsilon_{yi}(t_{ij}) \perp\!\!\!\perp \mathbf{b}_{yi}, \epsilon_{xi}(t_{ij}) \perp\!\!\!\perp \mathbf{b}_{xi}$$

- Association measured via $\mathbf{D}$ and Σ_i.

Model 2 on Pain Data

Random Intercept Model

$$\begin{cases} Tolerance_i(t_{ij}) = \beta_0^t + \beta_1^t \cdot sex_i + \beta_2^t \cdot ses_i + b_{i0}^t + \epsilon_{ij}^t \\ Rating_i(t_{ij}) = \beta_0^r + \beta_1^r \cdot sex_i + \beta_2^r \cdot ses_i + b_{i0}^r + \epsilon_{ij}^r \end{cases}$$

with

$$\begin{bmatrix} \mathbf{b}_{yi} \\ \mathbf{b}_{xi} \end{bmatrix} \sim \mathcal{N}_2 \left[\mathbf{0}, \begin{pmatrix} \sigma_y^2 & \sigma_{y,x} \\ \sigma_{y,x} & \sigma_x^2 \end{pmatrix} \right]; \quad \begin{bmatrix} \epsilon_{yi} \\ \epsilon_{xi} \end{bmatrix} \sim \mathcal{N}_2 \left[\mathbf{0}, \mathbf{I}_2 \right]$$

$$\epsilon_{yi}(t_{ij}) \perp\!\!\!\perp \mathbf{b}_{yi}, \epsilon_{xi}(t_{ij}) \perp\!\!\!\perp \mathbf{b}_{xi}$$

Model 2 on Pain Data: LMER+NLME

```
model_lmer<-lmer(value~ variable+variable:sex+variable:ses-1+
             (variable-1|id), na.action=na.omit,
             data=data_long_melted)

model_lme<-lme(value~variable+variable:sex+variable:ses-1,
            random = ~0+variable | id, data=data_long_melted,
            na.action=na.omit)
```

Model 2 on Pain Data: MCMCglmm

```
prior = list(R = list(V = diag(2), n = 4),
             G = list(G1=list(V = matrix(c(10,-0.50,-0.50, 0.45),
             nrow=2), n = 1)))

m_pain<-MCMCglmm(cbind(pain_tolerance, pain_rating) ~
         trait+trait:sex+trait:ses - 1,
         random = ~ us(trait):units, rcov = ~ idh(trait):units,
         family = rep("gaussian", 2),prior=prior, nitt = 10000,
         burnin = 1000, thin=25, data = data_long)
```

Model 2 on Pain Data: INLA

```
formula.model_2=Y~ -1+
  f(Intercept1, model='linear', mean.linear = 0, prec.linear = 0.001
  f(Intercept2, model='linear', mean.linear = 0, prec.linear = 0.001
  f(ses1, model='linear', mean.linear = 0, prec.linear = 0.001)+
  f(ses2, model='linear', mean.linear = 0, prec.linear = 0.001)+
  f(sex1, model='linear', mean.linear = 0, prec.linear = 0.001)+
  f(sex2, model='linear', mean.linear = 0, prec.linear = 0.001)+
  f(ID1, model="iid2d", n=2*63, hyper = list(theta =
  list(prior = "wishart2d",param=c(1,10,0.45, -0.50))))

final_model_2<-inla(formula.model_2, family = c("gaussian",
                    "gaussian"),data =final_data, verbose=TRUE)
```

Model 2 on Pain Data: Results

	lmer	lmer_sd	nlme	nlme_sd	INLA	INLA_sd	MCMC	MCMC_sd
beta_0^t	4.87	0.70	4.87	0.70	4.57	0.69	4.86	0.41
beta_sf^t	0.22	0.18	0.22	0.18	0.22	0.16	0.22	0.11
beta_ses^t	-0.02	0.01	-0.02	0.01	-0.02	0.01	-0.02	0.01
beta_0^r	7.11	1.75	7.11	1.75	7.22	1.43	6.96	1.08
beta_sf^r	-0.33	0.44	-0.33	0.44	-0.29	0.34	-0.29	0.29
beta_ses^r	-0.02	0.02	-0.02	0.02	-0.02	0.02	-0.02	0.02
u_t^2	0.10		0.10		0.35		0.43	
u_r^2	2.43		2.43		0.46		2.70	
rho_rt	-0.49		-0.49		-0.11		-0.26	

Method 2: Sources

- Books
  - G. Fitzmaurice, M. Davidian, G. Verbeke, Longitudinal Data Analysis, 2009, Chapters 13 & 16
- Papers
  - S. Fieuws, G. Verbeke, Pairwise Fitting of Mixed Models for the Joint Modeling of Multivariate Longitudinal Profiles, 2006, Biometrics
  - G. Verbeke, S. Fieuws, The analysis of multivariate longitudinal data: A review, 2012, Stat Methods Med Res

Method 3: Joint Mixed Model with latent variable

Joint Mixed Model with latent variable

$$
\begin{cases}
x_i(t_{ij}) = m_i(t_{ij}) + \epsilon_{xi}(t_{ij}) \\
y_i(t_{ij}) = \mathbf{w}_{yi}^{\mathsf{T}}\alpha_{\mathbf{y}} + \gamma \cdot m_i(t_{ij}) + \mathbf{v}_{yi}^{\mathsf{T}}(t_{ij})\beta_{\mathbf{y}} + \mathbf{z}_{yi}^{\mathsf{T}}(t_{ij})\mathbf{b}_{yi} + \epsilon_{yi}(t_{ij})
\end{cases}
$$

with

$$m_i(t_{ij}) = \mathbf{w}_{xi}^{\mathsf{T}}\alpha_{\mathbf{x}} + \mathbf{v}_{xi}^{\mathsf{T}}(t_{ij})\beta_{\mathbf{x}} + \mathbf{z}_{xi}^{\mathsf{T}}(t_{ij})\mathbf{b}_{xi}$$

and

$$\mathbf{b}_{xi} \sim \mathcal{N}(\mathbf{0}, \mathbf{D}_x), \mathbf{b}_{yi} \sim \mathcal{N}(\mathbf{0}, \mathbf{D}_y)$$

$$\epsilon_{yi}(t_{ij}) \sim \mathcal{N}_{n_i}(\mathbf{0}, \sigma_y^2), \epsilon_{xi}(t_{ij}) \sim \mathcal{N}_{n_i}(\mathbf{0}, \sigma_x^2)$$

$$\epsilon_{yi}(t_{ij}) \perp\!\!\!\perp \mathbf{b}_{yi}, \epsilon_{xi}(t_{ij}) \perp\!\!\!\perp \mathbf{b}_{xi}$$

Model 3 on Pain Data

Random ses + Intercept Model

$$\begin{cases} Tolerance_i(t_{ij}) = \beta_0^t + b_1^t \cdot ses_i + b_{i0}^t + \epsilon_{ij}^t \\ Rating_i(t_{ij}) = \beta_0^r + \gamma_1 \cdot b_1^t \cdot ses_i + \gamma_2 \cdot b_{i0}^t + \epsilon_{ij}^r \end{cases}$$

Model 3 on Pain Data: INLA

```
formula.model_3=Y~-1+
   f(Intercept1, model='linear')+
   f(Intercept2, model='linear')+
   f(sestol, ses, hyper=list(prec= list(initial=0, fixed=TRUE))) +
   f(sesrat, ses, copy="sestol",hyper=list(beta=list(fixed=FALSE)))+
   f(idtol, ID, hyper=list(prec = list(initial=0, fixed=TRUE))) +
   f(idrat, ID, copy="idtol",hyper = list(beta=list(fixed=FALSE)))

final_model_3<-inla(formula.model_3,
                    family = c("gaussian","gaussian"),
                    data = final_data, verbose=TRUE)
```

Model 3 on Pain Data: Results

	INLA	INLA_sd
beta_0^t	3.15746	0.09438
b_ses^t	0.00005	0.00000
b_0^t	0.00004	0.00000
beta_0^r	5.37924	0.17334
gamma_1	0.99521	0.31614
gamma_2	1.04291	0.31116

Method 3: Sources

- https://groups.google.com/g/r-inla-discussion-group/c/ClNVlx1lgwY
- https://arxiv.org/pdf/1210.0333.pdf

Method 1: Multivariate Normal Model

Multivariate Normal Model

$$\begin{cases} y_i(t_{ij}) = \mathbf{v}_{yi}^{\mathsf{T}}(t_{ij})\beta_{\mathbf{y}} + \epsilon_{yi}(t_{ij}) \\ x_i(t_{ij}) = \mathbf{v}_{xi}^{\mathsf{T}}(t_{ij})\beta_{\mathbf{x}} + \epsilon_{xi}(t_{ij}) \end{cases}$$

with

$$\begin{bmatrix} \epsilon_{yi} \\ \epsilon_{xi} \end{bmatrix} \sim \mathcal{N}_{n_i}(\mathbf{0}, \Sigma_i)$$

- Association measured via Σ_i

Model 1 on Pain Data

Random Intercept Model

$$\begin{cases} Tolerance_i(t_{ij}) = \beta_0^t + \beta_1^t \cdot sex_i + \beta_2^t \cdot ses_i + \epsilon_{ij}^t \\ Rating_i(t_{ij}) = \beta_0^r + \beta_1^r \cdot sex_i + \beta_2^r \cdot ses_i + \epsilon_{ij}^r \end{cases}$$

with

$$\begin{bmatrix} \epsilon_{yi} \\ \epsilon_{xi} \end{bmatrix} \sim \mathcal{N}_2\left[\mathbf{0}, \text{Unstructured}_8\right]$$

Model 1 on Pain Data: INLA

```
gls_unstructured<-gls(value~variable+variable:ses+variable:sex-1,
                  correlation=corSymm(form=~1|id),
                  weights= varIdent(form=~1|Period),
                  data=data_long_melted, na.action=na.omit)
```

```
m_pain<-MCMCglmm(cbind(pain_tolerance, pain_rating) ~
        trait+trait:sex+trait:ses - 1,
        rcov = ~ us(Period:trait):units,
        family = rep("gaussian", 2),prior=prior,
        nitt = 10000, burnin = 1000,
            thin=25, data = data_long)
```

Model 1 on Pain Data: Results

	gls	gls_sd	MCMCglmm	MCMCglmm_sd
beta_0^t	5.25	0.00	5.30	0.03
beta_sf^t	0.82	0.01	0.24	0.01
beta_ses^t	-0.03	0.06	-0.03	0.00
beta_0^r	7.50	0.00	6.70	0.32
beta_sf^r	-0.54	0.07	-0.62	0.05
beta_ses^r	-0.02	0.25	-0.01	0.01

Model 1 Results

Marginal variance covariance matrix

	[,1]	[,2]	[,3]	[,4]	[,5]	[,6]	[,7]	[,8]
[1,]	1.000000	0.9646700	0.934000	0.880790	-0.146390	0.31915	0.011592	0.0085110
[2,]	0.964670	1.0000000	0.915690	0.897470	-0.084704	0.31812	0.077383	0.0020768
[3,]	0.934000	0.9156900	1.000000	0.923760	-0.183270	0.28127	-0.034945	-0.0365370
[4,]	0.880790	0.8974700	0.923760	1.000000	-0.135120	0.24249	0.020602	-0.0749610
[5,]	-0.146390	-0.0847040	-0.183270	-0.135120	1.000000	0.53617	0.435130	0.2272000
[6,]	0.319150	0.3181200	0.281270	0.242490	0.536170	1.00000	0.373270	0.2487200
[7,]	0.011592	0.0773830	-0.034945	0.020602	0.435130	0.37327	1.000000	0.3341800
[8,]	0.008511	0.0020768	-0.036537	-0.074961	0.227200	0.24872	0.334180	1.0000000

Standard Deviations: 1 1 1 1 1 1 1 1

	[,1]	[,2]	[,3]	[,4]	[,5]	[,6]	[,7]	[,8]
[1,]	1.0000000	0.7923632234	0.2757604	-0.16859774	-0.32375237	0.3394998084	0.7253773	0.53763412
[2,]	0.7923632	1.0000000000	0.4762324	0.06301609	-0.58650226	-0.0005261689	0.6880497	0.60665062
[3,]	0.2757604	0.4762324384	1.0000000	0.76345228	-0.47261506	0.3155500984	-0.1407778	0.44914344
[4,]	-0.1685977	0.0630160916	0.7634523	1.00000000	-0.01470108	0.1720782933	-0.4947750	-0.06233257
[5,]	-0.3237524	-0.5865022575	-0.4726151	-0.01470108	1.00000000	0.1274419714	-0.3406734	-0.74698798
[6,]	0.3394998	-0.0005261689	0.3155501	0.17207829	0.12744197	1.0000000000	0.1558983	0.16098986
[7,]	0.7253773	0.6880497328	-0.1407778	-0.49477504	-0.34067340	0.1558983051	1.0000000	0.58234240
[8,]	0.5376341	0.6066506239	0.4491434	-0.06233257	-0.74698798	0.1609898619	0.5823424	1.00000000

Method 1: Sources

- Usually mentioned briefly as introduction
- Books
  - G. Fitzmaurice, M. Davidian, G. Verbeke, Longitudinal Data Analysis, 2009, Chapters 13
- Papers
  - H. Cho, The analysis of multivariate longitudinal data using multivariate marginal models, Journal of Multivariate analysis, 2016
  - G. Verbeke, S. Fieuws, The analysis of multivariate longitudinal data: A review, 2012, Stat Methods Med Res

To-do

- Elaborate on model 3 using INLA predictor matrix
- Use AR and generic random effects to simulate correlated residuals
- Understand why results with MCMCglmm and INLA differ

- H. Rue, S. Martino, Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations, 2009, JRSS B
- J. van Niekerk, H. Bakka, H. Rue, Joint models as latent Gaussian models - not reinventing the wheel, 2019, arXiv
- J. van Niekerk, H. Bakka, H. Rue, Competing risks joint models using R-INLA, 2021, Statistical Modelling
- R. Weiss, Modelling Longitudinal Data, 2005, Chapter 13