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# Bayesian Analysis of GLMMs Using PROC BGLIMM Walt Stroup, University of Nebraska-Lincoln

Bio:

Emeritus Professor of Statistics, University of Nebraska-Lincoln.
Co-author SAS for Mixed Models (1996, 2006, 2018).
Author Generalized Linear Mixed Models (2013).
Teaching & Research specializations: statistical modeling, design of experiments, collaboration with allied disciplines ("consumers of statistical methods").
ASA Fellow. Founding chair: UNL Department of Statistics.

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#### Outline

#### I. GLMM Basics

- A. Defining Elements of a GLMM
- B. Overview of Bayesian Estimation and Inference for GLMMs

#### II. Three Examples

- A. Multi-Clinic Binomial (Beitler-Landis Data from SAS MM 2018 ed, Ch 11)
  - i. Preliminary PROC BGLIMM run
  - ii. Diagnostics
  - iii.Needed options
  - iv.Revised PROC BGLIMM run, useable analysis, interpretation
  - v. Post-processing steps (equivalent of ILINK in PROC GLIMMIX)
- B. Multi-level (a.k.a. split-plot or hierarchical) with count data (SAS MM Ch 13)
- c. Repeated measures (a.k.a. longitudinal) (SAS MM, Ch 8)

### Generalized Linear Mixed Model (GLMM) Setting

**Response Variable Distribution - Model Effect Combinations** 

ſ	Class	ic Statistical	systematic/explanatory		ran	dom/residual
	Мос	lel Format:	Χβ		Zb	
	re systematic	sponse = + random/residual	Categorical	continuous		Residual error
	res	ponse variable	e.g. $\mu + \tau_i$	e.g. $\beta_0 + \beta_1 X$	model effects	structure (e.g. serial/spatial)
	Gaussian (normal)					"R-side"
		discrete proportion binomial multinomial				
	Non-	continuous proportion beta				"C side"
	Gaussian	count Poisson negative Binomial				G-side
		time to event				
#SASGF		etc				SAS' GLOBAL FORUM 202

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## **Defining Elements of a GLMM**

- η = g(μ) = Xβ + Zb (link function = linear predictor)
  b~N(0,G)
- $y|b \sim \mathcal{D}(\mu, \Sigma)$

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• 
$$\Sigma = V_{\mu}^{1/2} R V_{\mu}^{1/2}; V_{\mu}^{1/2} = diag[v(\mu)]$$

• **R** is scale matrix, e.g.  $\mathbf{R} = \mathbf{I}\boldsymbol{\phi}$  or repeated measures covariance

• log likelihood 
$$(y|b) \propto exp\left[\frac{y\theta - b(\theta)}{\phi}\right]$$

• 
$$\mu = \frac{\partial b(\theta)}{\partial \theta}; v(\mu) = \frac{\partial^2 b(\theta)}{\partial \theta^2}; Var(y|b) = \phi v(\mu)$$

• canonical parameter  $\theta(\mu) \rightarrow \theta_{\eta} = \theta[g^{-1}(X\beta + Zb)]$ 

## **GLMM Estimation and Inference**

- Frequentist approach: maximum likelihood
- Log likelihood:
  - $\log[f(y;\beta)]$
  - $f(y;\beta) = \int_{b} f(y;\beta|b)f(b)db$
- Log likelihood generally intractable
  - Linearization pseudo-likelihood in PROC GLIMMIX
  - Integral approximation quadrature or Laplace (GLIMMIX, NLMIXED)
- Obtain estimates and standard errors
  - Pseudo-likelihood allows REML (or REML-like) covariance estimates
  - Use estimates & SE to compute test statistics or confidence intervals



## **Bayesian Estimation and Inference**

Posterior distribution (heuristic overview)

• 
$$f(\beta, \sigma | y, b) = \frac{f(y, b | \beta, \sigma) f(\beta, \sigma)}{\int f(y, b | \beta, \sigma) f(\beta, \sigma) d\beta d\sigma}$$

- $\sigma$  is vector of scale & covariance parameters to be estimated
- $f(y, b|\beta, \sigma)$  defined by GLMM distributions f(y|b), f(b)
- Generally intractable: approximated by simulation
- Steps
  - specify GLMM [defines  $f(y, b | \beta, \sigma)$ ] and priors [define  $f(\beta, \sigma)$ ]
  - tuning
  - burn-in
  - sample posterior distribution  $\Rightarrow$  mean, median, quantiles, credible interval

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## Why Bayesian Methods & Not PROC GLIMMIX?

#### Academic Journals

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- some prefer Bayesian credible intervals to classical significance tests
- some require Bayesian analysis

#### More generally applicable reasons

- Frequentist MLE and Bayesian estimates with "non informative prior" are essentially equivalent
  - $\Rightarrow$  frequentist MLE implicitly assumes ignorance until data analyzed
  - (arguably) compromises efficiency and accuracy
- In reality, studies do not begin in complete ignorance
- In many cases, a study has been preceded by many similar studies
- Moderately informative priors allow us to "use what we know"

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## Example 1: Multi-clinic, Binomial Data

- Example 11.5, SAS for Mixed Models (2018)
- Beitler and Landis (Biometrics, 1985)
- Eight clinics; sample representative of target population
- Two treatments: CNTL and DRUG
- Two groups at each clinic,  $n_{ij}$  subjects assigned to  $i^{th}$ treatment at  $j^{th}$  clinic
- Response variable:  $y_{ij}$  = number of patients with favorable outcome out of  $n_{ij}$  in group



## **Blocked Designs**

#### Types

Multi-location, multi-center, multi-clinic

- > Matched pairs
- > Before and after on same subject

#### > Field plots

	▶ etc.		"Experiment" (study) design			Full design		
Visualization			Clinic Group		Clinic	Gro	oup	
			1			1	trt 1	trt 2
	Treatment designTrt 1Trt 2		2			2	trt 2	trt 1
			3			3	trt 2	trt 1
			4			4	trt 1	trt 2
			8			8	trt 2	trt 1



#### **Repurposed ANOVA**

Experiment		Treatme	ent	Combined	
Source	d.f.	Source	d.f.	Source	d.f.
clinic	7				7
		trt	1	trt	1
group(clinic)	8	"parallels" (Yates, Fisher, 1935)	14	group(clinic)   trt a.k.a. "residual" a.k.a "clinic x trt"	8-1=7
Total	15	Total	15	Total	15



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#### **Resulting Logit-normal GLMM**







#### FYI: Beta-binomial Mixed Model

combined

Source	d.f.	a iid $N(0 \sigma^2)$
clinic	7	$C_j \text{ I.i.u. } N(0, O_c)$
treatment	1	$ (\mu_{i}, \mu_{j}) $
group (clinic)   trt "residual"	7	Link: $\eta_{ij} = \log \left( \frac{\eta_{ij}}{1 - \mu_{ij}} \right)$
total	15	$y_{ij}   c_j, p_{ij} \sim \text{Ind Binomial}(N_{ij}, p_{ij})$ $p_{ij} \sim \text{beta}(\mu_{ij}, \varphi) \text{ or beta}(\alpha_{ij}, \beta_{ij})$ $\hat{\mu}_{ij} = 1 / \{1 + \exp[-(\hat{\tau}_i + \hat{c}_j)]\}$ $\alpha_{ij} = \mu_{ij}\varphi; \beta_{ij} = (1 - \mu_{ij})\varphi$

No  $ct_{ij}$  - "residual" info used to estimate  $\varphi$  (beta scale parameter) PROC BGLIMM requires Gaussian random effects;  $p_{ij}$  not Gaussian Beta-binomial model requires PROC MCMC (another time...)

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### **Re-purposed ANOVA and Sensible Model**

#### sensible model one-to-one ANOVA effect – model parameter match

combined		model				
Source	d.f.	LMM	naive GLMM	Logit-normal GLMM w/unit	Beta Binomial GLMM	Beta Binomial GLMM w/unit
clinic	7	C <sub>j</sub>	c <sub>j</sub>	C <sub>j</sub>	с <sub>ј</sub>	с <sub>ј</sub>
treatment	1	τ <sub>i</sub>	τ <sub>i</sub>	τ <sub>i</sub>	τ <sub>i</sub>	$\tau_{i}$
group   trt clinic x trt "residual"	7	$e_{ij}$ or $\sigma^2$	→ overdispersion likely	ct <sub>ij</sub>	φ	φ, ct <sub>ij</sub> confounded
total	15					





### **Re-purposed ANOVA and Sensible Model**

#### sensible model one-to-one ANOVA effect – model parameter match

combined			model			
Source	d.f.	LMM	naive GLMM	Logit-normal GLMM w/unit	Beta Binomial GLMM	Beta Binomial GLMM w/unit
clinic	7	c <sub>j</sub>	C,	C <sub>j</sub>	с <sub>ј</sub>	C <sub>j</sub>
treatment	1	$\tau_{i}$	τ	τ <sub>i</sub>	τ <sub>i</sub>	τ
group   trt clinic x trt "residual"	7	$e_{ij}$ or $\sigma^2$	→ overdispersion likelv	ct <sub>ij</sub>	ф	φ, ct <sub>ij</sub> confounded
total	15					





#### PROC BGLIMM statements for Example 1

#### PROC GLIMMIX

```
/* as shown in SAS MM 3 */
proc glimmix data=clinics;
  class clinic trt;
  model fav/Nij=trt;
  random intercept trt
    / subject=clinic;
  lsmeans trt / ilink diff
    oddsratio cl;
run;
```

PROC BGLIMM

```
proc bglimm data=clinics seed=81152097
    plots=(trace autocorr density)
    diagnostics=all outpost=cout
    statistics(percentage=(2.5 50 97.5)) dic;
    class clinic trt;
    model fav/Nij=trt;
    random intercept trt / subject=clinic;
    estimate 'cntl' intercept 1 trt 1 0;
    estimate 'drug' intercept 1 trt 0 1;
    estimate 'log odds ratio' trt 1 -1;
    ods output estimates=model_scale;
run;
```



## **PROC BGLIMM Diagnostics**

- Trace (a.k.a. "Caterpillar") and autocorrelation plots
- Geweke
  - compares estimates from early and late iterations
  - must be "acceptably similar"
- Heidelberger-Welch
  - stationarity test
  - half-width test does sample size provide acceptable parameter estimate accuracy?
- Raftery-Lewis
  - addresses accuracy of posterior distribution's percentile estimates
  - Dependence factor measures posterior sample independence ( $\cong 1$  is ideal)
- Effective Sample Size
  - autocorrelation in sampling algorithm limits efficiency
  - number of samples taken versus adjusted number after accounting for autocorrelation

### Plots from BGLIMM Run with Defaults



Autocorr: quickly  $\rightarrow$  0 as lag increases



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## Worrisome Diagnostics from Default Run, 1 of 3

Heidelberger-Welch Diagnostics										
		rity Test		Half-Width Test						
	Cramer-von		Test	Iterations			Relative	Test		
Parameter	Mises Stat	p-Value	Outcome	Discarded	Half-Width	Mean	Half-Width	Outcome		
Intercept	0.0951	0.6092	Passed	0	0.0875	-0.4288	-0.2041	Failed		
trt cntl	0.2343	0.2098	Passed	0	0.0630	-0.9815	-0.0641	Passed		
trt drug										
Random VC(1)	0.2008	0.2659	Passed	2000	0.0655	1.8446	0.0355	Passed		
Random VC(2)	0.0432	0.9160	Passed	0	0.0855	1.2928	0.0661	Passed		

Raftery-Lewis Diagnostics										
Quantile=0.025 Accuracy=+/-0.005 Probability=0.95 Epsilon=0.001										
	Nu	mber of Samp	les	Dependence						
Parameter	Burn-In	Total	Minimum	Factor						
Intercept	29	32909	3746	8.7851						
trt cntl	18	19114	3746	5.1025						
trt drug		-								
Random VC(1)	4	4636	3746	1.2376						
Random VC(2)	4	4714	3746	1.2584						

Dependence Factor Ideally should be close to one with all due respect to rules of thumb should not be > 4





#### Worrisome Diagnostics from Default Run, 2 of 3

Effective Sample Sizes									
		Autocorrelation							
Parameter	ESS	Time	Efficiency						
Intercept	174.1	28.7273	0.0348						
trt cntl	301.6	16.5782	0.0603						
trt drug									
Random VC(1)	886.7	5.6389	0.1773						
Random VC(2)	722.3	6.9225	0.1445						

ESS should be >> 1000 (at least!) Poor efficiency caused by autocorrelation at high lags

Posterior Summaries and Intervals									
			Standard	95%	HPD				
Parameter	Ν	Mean	Deviation	Inte	rval				
Intercept	5000	-0.4288	0.5298	-1.4832	0.6182				
trt cntl	5000	-0.9815	0.5507	-2.0139	0.1325				
trt drug	0								
Random VC(1)	5000	1.9221	1.2313	0.4006	4.2354				
Random VC(2)	5000	1.2928	1.0545	0.2264	3.1124				

"VC(2)" is  $\hat{\sigma}_{ct}^2$ in GLIMMIX  $\hat{\sigma}_{ct}^2 \cong 0.02$ 1.29 implausibly high





#### Worrisome Diagnostics from Default Run, 3 of 3

PROC BG default start	s vs.	PRO	C GLIN plutio	MMIX ns	
Initial Valu Fixed Ef		Solutio	ons fo Effect:	r Fixed s	
Parameter	Value		Effect	trt	Estimat
Intercept	-0.3102		Intercept		-0.457
trt cntl	-0.4040		trt	cntl	-0.746

Geweke Diagnostics								
Parameter	z	Pr >  z						
Intercept	-0.4815	0.6302						
trt cntl	-0.2990	0.7649						
trt drug								
Random VC(1)	0.5412	0.5884						
Random VC(2)	0.9604	0.3369						

Okay in this run But always check





## Why problems Occur

- Inadequate number of burn-in iterations
- Inadequate sampling of posterior distribution
- Inadequate thinning ( $\Rightarrow$  autocorrelation)
- Inappropriate prior distributions
  - "Flat" a.k.a. "non-informative" priors often include implausible values
  - Default prior may "look where the parameter is not"

Model Information		Priors for Fixed		Priors for Scale and Covariance Parameters		
Burn-In Size	500	Effe	cts	Parameter	Prior	
Simulation Size	5000	Parameter	Prior	Random Cov (Diag)	Inverse Gamma (Shape=2, Scale=2)	
Thinning	1	Intercept	Constant			
		trt cntl	Constant			





## **Default Prior**

- Inverse gamma (shape=2, scale=2)
- Most likely values (e.g. obtain from GLIMMIX run)
  - clinic variance  $(\sigma_c^2)$  **2.0**
  - clinic × treatment variance ( $\sigma_{ct}^2$ ) <0.1
- Plot of inv-gamma(2,2)





## Selection of "use what you know" priors

- Method suggested by Christiansen, et al. (2011)
- Specify the following
  - most likely value of parameter
  - extremes below or above which parameter value implausible
- Find distribution
  - whose mode  $\cong$  most likely value
  - whose  $1^{st}$  and  $99^{th}$  quantiles  $\cong$  upper and lower extremes
- Typical approach for variance
  - use precision = 1/variance
  - inv-gamma prior for variance  $\Rightarrow$  gamma prior for precision

# Christiansen, et al. method for $\sigma_{ct}^2$

#### Most likely value

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- GLIMMIX default (pseudo-likelihood)  $\hat{\sigma}_{ct}^2 = 0.06$
- GLIMMIX quadrature  $\hat{\sigma}_{ct}^2 = 0.01$
- $\Rightarrow$  most likely value for precision between 16.7 and 100

#### Example program to identify candidate priors

```
data gamma_prior;
mode=40;
/* A=shape parameter */
/* B=scale parameter */
do a=1.01,1.05,1.1,1.25,1.5,2,3,5,10,20;
b=mode/(a-1);
do prec=0 to 200;
var=1/prec;
pdf_gamma=pdf("gamma",prec,a,b);
cdf_gamma=cdf("gamma",prec,a,b);
output;
end;
end;
```

```
proc sort data=gamma_prior; by a;
proc print;
where (0.008<cdf_gamma<0.012
or 0.988<cdf_gamma<0.992);
run;
proc gplot data=gamma_prior;
by a;
plot pdf_gamma*prec/href=40;
plot cdf_gamma*prec/vref=0.01,0.99;
run;
```



#### Trial-and-error result

- Gamma(shape=3, scale=20)
- translates to inv-gamma(shape=3,scale=0.05) for  $\sigma_{ct}^2$

plots







## **Revised PROC BGLIMM**

New options in **bold**

#### Increase

- burn-in: NBI,
- posterior sampling: NMC
- thinning: THIN

#### Priors

- for TRT effects  $\eta$ ,  $\tau_{CNTL}$ 
  - LIST: starting values
    COEFFPRIOR: N(0, VAR)
- for variance of random effect: COVPRIOR
- Output for post-processing
  - OUTPOST

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ODS OUTPUT

proc bglimm data=clinics seed=81152097 nbi=2500 nmc=100000 thin=10 plots=(trace autocorr density) diagnostics=all dic outpost=cout; class clinic trt; model fav/Nij=trt / init=(**list=(-0.46 -0.75)** pinit) coeffprior=normal(var=9); random intercept / subject=clinic covprior=igamma(shape=1.5, scale=1); random trt / subject=clinic covprior=igamma(shape=3, scale=0.05); estimate "CNTL" intercept 1 trt 1 0; estimate "DRUG" intercept 1 trt 0 1; estimate "log odds-ratio" trt 1 -1; ods output estimates=model scale; title "BGLIMM - all needed options"; run;

#### Selected Diagnostic Listing

Effective Sample Sizes						
		Autocorrelation				
Parameter	ESS	Time	Efficiency			
Intercept	2952.3	3.3872	0.2952			
trt cntl	10000.0	1.0000	1.0000			
trt drug						
Random1 Var	7644.9	1.3081	0.7645			
Random2 Var	8756.1	1.1421	0.8756			

	Raftery-Lewis Diagnostics						
Quantile=0.	025 Accuracy=	+/-0.005 Proba	ability=0.95 Ep	silon=0.001			
	Nu	mber of Samp	les	Dependence			
Parameter	Burn-In	Total	Minimum	Factor			
Intercept	6	6350	3746	1.6951			
trt cntl	2	3834	3746	1.0235			
trt drug							
Random1 Var	2	3803	3746	1.0152			
Random2 Var	2	3650	3746	0.9744			









## **Posterior Summary Listing**

#### Variance components

- $\hat{\sigma}_{c}^{2} = 2.1165$  (Random1)
- $\hat{\sigma}_{ct}^2 = 0.0261$  (Random2)
- With effects model
  - $\hat{\eta} = -0.4491$  estimates  $logit(\hat{p}_{DRUG})$
  - $\hat{\tau}_{CNTL} = -0.7454$  estimates  $log(odds \ ratio)$
- HPD
  - "highest posterior density"
  - narrowest credible interval

P	Posterior Summaries and Intervals						
			Standard				
Parameter	Ν	Mean	Deviation	95% HPD	Interval		
Intercept	10000	-0.4491	0.5504	-1.6003	0.5728		
trt cntl	10000	-0.7454	0.3053	-1.3201	-0.1303		
trt drug	0						
Random1 Var	10000	2.1165	1.5208	0.3744	4.6572		
Random2 Var	10000	0.0261	0.0281	0.00444	0.0639		

Results from ESTIMATE Statements						
		Standard				
Label	Mean	Deviation	95% HPD	Interval		
CNTL	-1.1946	0.5612	-2.3136	-0.0881		
DRUG	-0.4491	0.5504	-1.6003	0.5728		
log odds-ratio	-0.7454	0.3053	-1.3201	-0.1303		

analog to 95% confidence interval





#### **Posterior percentiles**

- Add STATISTICS option to PROC statement
- "50" (50<sup>th</sup> percentile) = median (alternative est)
- "2.5" and "97.5" percentiles give symmetric credible interval

```
proc bglimm data=clinics seed=81152097
nbi=2500 nmc=100000 thin=10
plots=(trace autocorr density)
diagnostics=all
statistics(percent=(2.5 50 97.5))
outpost=cout;
```

	Posterior Summaries							
			Standard	P	ercentile	S		
Parameter	Ν	Mean	Deviation	2.5	50	97.5		
Intercept	10000	-0.4491	0.5504	-1.5574	-0.4418	0.6304		
trt cntl	10000	-0.7454	0.3053	-1.3539	-0.7410	-0.1619		
trt drug	0							
Random1 Var	10000	2.1165	1.5208	0.6293	1.7386	5.7644		
Random2 Var	10000	0.0261	0.0281	0.00701	0.0193	0.0845		





#### Post-processing

- PROC BGLIMM ESTIMATE statement has no ILINK option
- To obtain **data scale** estimates & intervals, e.g.
  - $\hat{p}_{CNTL}$
  - $\hat{p}_{DRUG}$
  - odds ratio
- Use post-processing data steps
- Two approaches
  - OUTPOST and %SUMINT macro
  - ODS OUTPUT and follow-up DATA step
  - OUTPOST uses posterior sample data set , ODS uses summary statistics

#### Post-processing 1: OUTPOST + %SUMINT

 Post-processing statements use OUTPOST=COUT

#### Listing

Posterior Summaries and Intervals							
			Standard	95%	HPD		
Parameter	Ν	Mean	Deviation	Inte	rval		
OddsRatio	10000	0.4970	0.1532	0.2251	0.8004		
pr_cntl	10000	0.2461	0.0990	0.0750	0.4475		
pr_drug	10000	0.3965	0.1224	0.1679	0.6394		
ProbDiff	10000	0.1504	0.0667	0.0248	0.2800		





#### Post-processing 2

 Post-processing statements using ODS OUTPUT data set

```
data datascale;
set modelscale;
if label='CNTL'
    or label='DRUG';
prob=1/(1+exp(-Mean));
lower=1/(1+exp(-HPDLower));
upper=1/(1+exp(-HPDUpper));
```

data oddsratio; set modelscale; if label='log odds\_ratio'; OddsRatio=exp(Mean); lower=exp(HPDLower); upper=exp(HPDUpper); proc print data=datascale; proc print data=oddsratio; run;

Obs	Label	Mean	StdDev	<b>HPDLower</b>	<b>HPDUpper</b>	prob	lower	upper
1	CNTL	-1.1946	0.5612	-2.3136	-0.0881	0.23245	0.09001	0.47798
2	DRUG	-0.4491	0.5504	-1.6003	0.5728	0.38957	0.16793	0.63942



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Obs Label	Mean	StdDev	<b>HPDLower</b>	<b>HPDUpper</b>	<b>OddsRatio</b>	lower	upper
1 log odds-ratio	-0.7454	0.3053	-1.3201	-0.1303	0.47452	0.26712	0.87780



# Example 2

- Split-plot Experiment
  - Whole Plot Factor METHOD 2 levels
  - Whole Plots in 6 fields
  - Split Plot Factor MIX 2 levels
- Count Data
- SAS for Mixed Models (2018)
- Section 13.3.4

Field	W P	Treati	nents
1	1	11	12
I	2	21	22
2	3	11	12
2	4	21	22
2	5	11	12
3	6	21	22
4	7	11	12
4	8	21	22
5	9	11	12
Э	10	21	22
6	11	11	12
Ö	12	21	22





#### **Re-purposed ANOVA Sources of Variation**

Experiment	Design	Trt Design		Combined	
Source	d.f.	Source	d.f.	Source	d.f.
field	5			field	5
		method	1	method	1
wp(field)	6			wp(field)   method a.k.a. field x method	6-1=5
		mix	1	mix	1
		method x mix	1	method x mix	1
sp(wp)	12	"parallels"	20	sp(wp)   mix, method a.k.a. sp error	12-2=10
Total	23	Total	23	Total	23

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#### Poisson-gamma Process $\Rightarrow$ Negative Binomial GLMM



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#### **Negative Binomial GLMM**



Linear Predictor  $\eta + \alpha_i + \beta_j + (\alpha \beta)_{ii} + \mathbf{b}_{\mathbf{k}} + \mathbf{w}_{i\mathbf{k}}$  $\mathbf{b}_{\mathbf{k}}$  i.i.d.  $N(0, \sigma_B^2)$  $\mathbf{w}_{ik}$  i.i.d.  $N(0, \sigma_W^2)$  $y_{iik} | b_k, w_{ik} \sim \text{Neg Bin}(\lambda_{ijk}, \phi)$ Log Link  $\eta_{iik} = \log(\lambda_{iik})$ 

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#### Neg Bin GLMM – cell means (full rank) form

Combine	d	
Source	d.f.	
field	5	٦
method	1	
wp(blk)   method a.k.a.		
field x method	6-1=5	
mix	1	
method x mix	1	
sp(wp)   method, mix		
a.k.a. sp error	12-2=10	
Total	23	

Linear Predictor  

$$\eta_{ij} + \mathbf{b_k} + \mathbf{w_{ik}}$$

$$\mathbf{b_k} \text{ i.i.d. } N\left(0, \sigma_B^2\right)$$

$$\mathbf{w_{ik}} \text{ i.i.d. } N\left(0, \sigma_W^2\right)$$

$$y_{ijk} \mid b_k, w_{ik} \sim \text{Neg Bin}\left(\lambda_{ijk}, \phi\right)$$
Log Link  

$$\eta_{ijk} = \log\left(\lambda_{ijk}\right)$$

$$\eta_{ij} \text{ replaces } \eta + \alpha_i + \beta_j + \alpha\beta_{ij}$$

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#### **PROC BGLIMM Statements**

```
proc bglimm data=sp counts plots=(trace autocorr density)
   seed=20210107 diagnostics=all dic
   nbi=2500 nmc=500000 thin=50 outpost=model scale;
 class field method MeMx;
 model count=MeMx / noint distribution=negbin
   init=(list=(2.5, 2.9, 0.8, 2.0)) scaleprior=gamma(shape=20, iscale=25);
 random intercept method/ subject=field
   covprior=igamma(shape=4, scale=3);
 estimate "LSM 11" MeMx 1 0 0 0;
 estimate "LSM 12" MeMx 0 1 0 0;
 estimate "LSM 21" MeMx 0 0 1 0;
 estimate "LSM 22" MeMx 0 0 0 1;
 estimate "interaction" MeMx 1 -1 -1 1;
 estimate "Method Main Effect" MeMx 1 1 -1 -1 / divisor=2;
 estimate "Mix Main Effect" MeMx 1 -1 1 -1 / divisor=2;
 ods output estimates=link scale;
 title "Negative Binomial GLMM";
run;
```



#### **BGLIMM** Results

 Diagnostics okay (not shown here)

Listing

Posterior Summaries and Intervals								
			Standard	95% HPD				
Parameter	Ν	Mean	<b>Deviation</b>	Interval				
MeMx 11	10000	2.6048	0.7728	1.0057	4.0540			
MeMx 12	10000	3.1033	0.7731	1.5136	4.5331			
MeMx 21	10000	1.1871	0.7130	-0.1965	2.6263			
MeMx 22	10000	2.3487	0.6749	1.0120	3.6709			
Scale	10000	0.7647	0.1675	0.4520	1.0961			
Random VC(1)	10000	1.5829	0.8921	0.4250	3.3169			
Random VC(2)	10000	0.9997	0.5746	0.2646	2.0805			

Results from ESTIMATE Statements								
		Standard	95% HPD					
Label	Mean	Deviation	Interval					
LSM_11	2.6048	0.7728	1.0057	4.0540				
LSM_12	3.1033	0.7731	1.5136	4.5331				
LSM_21	1.1871	0.7130	-0.1965	2.6263				
LSM_22	2.3487	0.6749	1.0120	3.6709				
interaction	0.6631	0.8228	-1.0406	2.2255				
Method Main Effect	1.0861	0.6229	-0.1337	2.3246				
Mix Main Effect	-0.8301	0.4030	-1.6100	-0.0423				



#### Post-processing 1: with OUTPOST

```
data data_scale;
set model_scale;
Lambda_11=exp(MeMx_11);
Lambda_12=exp(MeMx_12);
Lambda_21=exp(MeMx_21);
Lambda_22=exp(MeMx_22);
Method_Diff_Ratio=
exp(Method_Main_Effect);
Mix_Diff_Ratio=
exp(Mix_Main_Effect);
```

```
%sumint(data=data_scale,
var=Lambda_11: Lambda_12:
Lambda_21: Lambda_22:
Method_Diff_Ratio:
Mix_Diff_Ratio)
```

Posterior Summaries and Intervals								
			Standard	95% HPD				
Parameter	Ν	Mean	Deviation	Interval				
Mix_Diff_Ratio	10000	0.4725	0.1947	0.1613	0.8636			
Lambda_11	10000	18.4369	19.2826	1.1794	48.0516			
Lambda_12	10000	30.4441	32.9238	2.0594	78.4440			
Lambda_21	10000	4.2326	3.5203	0.2555	10.5415			
Lambda_22	10000	13.2038	10.5077	1.2347	32.7550			
Method_Diff_Ratio	10000	3.6258	3.0682	0.5600	8.5199			





#### Post-processing 2: ODS OUTPUT + data steps

```
data LS means;
 set link scale;
 if label="LSM 11" or
 label="LSM 12" or
 label="LSM 21" or
 label="LSM 22";
 Lambda Est=exp(Mean);
 Lambda Lower=exp(HPDLower);
 Lambda Upper=exp(HPDUpper);
 title "Method x Mix LSMeans";
proc print data=LS means;
run;
data diff ratios;
 set link scale;
if label="Method Main Effect" or
 label="Mix Main Effect":
 Ratio Est=exp(Mean);
 Ratio Lower=exp(HPDLower);
 Ratio Upper=exp(HPDUpper);
 title "Diff Ratios";
proc print data=diff ratios;
run;
```

Obs	Label	Lambda_Est	Lambda_Lower	Lambda_Upper
1	LSM_11	13.5282	2.73376	57.6280
2	LSM_12	22.2715	4.54289	93.0480
3	LSM_21	3.2776	0.82158	13.8230
4	LSM_22	10.4720	2.75115	39.2874

Obs	Label	Ratio_Est	Ratio_Lower	Ratio_Upper
1	Method Main Effect	2.96279	0.87488	10.2222
2	Mix Main Effect	0.43603	0.19990	0.9586



# Example 3

- Repeated measures (a.k.a. longitudinal) data
- Example 8.2 in SAS for Mixed Models (2018)
  - data from Littell, Pendergast and Natarajan (2000)
  - also appears in SAS for Linear Models (2002) and PROC BGLIMM documentation
- Three treatments (labeled DRUG in data set)
  - two experimental nasal treatments (A and C)
  - one placebo (P)

#SASGE

- Response variable
  - FEV1 a measure of breathing comfort
  - Baseline measurement (BASEFEV) and at 0,1,2,...8 hours after treatment
- 24 patients assigned to each DRUG



#### **Re-purposed ANOVA Sources of Variation**

Experiment Design		Trt De	sign	Combined		
Source	d.f.	Source	Source d.f. Source		d.f.	
		drug	3-1=2	drug	2	
patient	72-1=71			patient  drug aka between	71-2=69	
		hour	8-1=7	hour	7	
		drug x hour	14	drug x hour	14	
occasion(patient)	72(8-1) = 504			occ(pt)   drug aka within	504-7-14= 483	
Total	576-1=575	Total	575	Total	575	

Linear Predictor:  $\eta_{ijk} = \alpha_i + \mathbf{s_{ij}} + \tau_k + (\alpha \tau)_{ik}$ Within:  $\begin{bmatrix} w_{ij1} & w_{ij2} & w_{ij3} & w_{ij4} & w_{ij5} & w_{ij6} \end{bmatrix}$  correlated



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## Interaction Plot, Objectives, PROC BGLIMM Statements

- FEV1: higher value ⇒ greater breathing comfort
- Objectives
  - do experimental drugs (A and C) improve breathing comfort relative to placebo (P)?
  - how long does improvement last?
  - objectives addressed by drug x hour effect
- BGLIMM Documentation
  - "model 2" fev1=basefev drug hour;
  - "model 3" fev1=basefev drug | hour;
  - documentation: "minor difference"
  - NOT minor: objective *requires* model 3!!



### **Alternative Models**

#### Generic Model

- $y|between \ subject \sim N(\mu, R)$
- between subject [patient(drug)]:  $s_{ij} \sim N(0, \sigma_s^2)$
- within subject covariance  $R = I_{72} \otimes R_{ij}$
- $R_{ij}$  is 8 × 8 covariance matrix, e.g. AR(1)
- Effects model for  $\mu$ 
  - $\eta + \beta X_{ij} + \alpha_i + \tau_k + \alpha \tau_{ik} + s_{ij}$ ;  $\alpha$ =drug;  $\tau$ =hour;  $X_{ij}$ =baseline FEV1
  - cell means version:  $\eta + \beta X_{ij} + \alpha \tau_{ik} + s_{ij}$
- Unequal slopes regression
  - $\eta + \beta X_{ij} + \alpha_i + \beta_i H + s_{ij}$ ; *H*=hour

#### PROC BGLIMM Statements – Effects Model Focus on Simple Effect of Drug at each Hour

```
proc bglimm data=fev1uni nmc=10000 seed=44672057
     plots=(trace autocorr density) diagnostics=all;
 class Drug Patient Hour;
 model FEV1 = BaseFev1 Drug|Hour;
 random int / subject=Patient;
 repeated Hour / subject=Patient(Drug) type=ar(1) r rcorr;
 estimate "A vs P at hour 1" Drug 1 0 -1 Drug*Hour 1 0 0 0 0 0 0 0
                                 0 0 0 0 0 0 0 0
                                         -1 0 0 0 0 0 0 0;
 estimate "C vs P at hour 1" Drug 0 1 -1 Drug*Hour 0 0 0 0 0 0 0 0
                                1000
                                         -1 0 0 0 0 0 0 0:
 0 -1 0 0 0 0 0;
 0 -1 0 0 0 0 0;
 0 0 -1 0 0 0 0;
 estimate "A vs P at hour 4" Drug 1 0 -1 Drug*Hour 0 0 0 1 0 0 0 0
                                0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0;
 estimate "C vs P at hour 4" Drug 0 1 -1 Drug*Hour 0 0 0 0 0 0 0 0 0
                                0 0 0 1 0 0 0 0 0 0 - 1 0 0 0;
 estimate "A vs P at hour 5" Drug 1 0 -1 Drug*Hour 0 0 0 0 1 0 0 0
                                0 0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0;
 estimate "C vs P at hour 5" Drug 0 1 -1 Drug*Hour 0 0 0 0 0 0 0 0
                                0 0 0 0 1 0 0 0
                                         0 0 0 0 -1 0 0 0;
 run;
```



#### Alternative Effects Model – Cell Means Form

#### obtain drug x hour LSMeans - coefficients from GLIMMIX LSMEANS E option

<pre>proc bglimm data=fev1uni nmc=10</pre>	<pre>proc bglimm data=fev1uni nmc=10000 seed=44672057 plots=(trace autocorr density) diagnostics=all;</pre>							
class Drug Patient Hour;								
<pre>model FEV1 = BaseFev1 Drug*Hour;</pre>								
<pre>random int / subject=Patient</pre>	;;							
repeated Hour / subject=Pati	.ent(Drug) type=ar(1) r rcorr;							
estimate "LSM A at hour 1"	intercept 1 basefev1 2.6493 Drug*Hour 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM C at hour 1"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0							
estimate "LSM P at hour 1"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM A at hour 2"	intercept 1 basefev1 2.6493 Drug*Hour 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM C at hour 2"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0							
estimate "LSM P at hour 2"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0;							
estimate "LSM A at hour 3"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM C at hour 3"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0							
estimate "LSM P at hour 3"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0;							
estimate "LSM A at hour 4"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM C at hour 4"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0							
estimate "LSM P at hour 4"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM A at hour 5"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM C at hour 5"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0							
estimate "LSM P at hour 5"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM A at hour 6"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM C at hour 6"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM P at hour 6"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM A at hour 7"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM C at hour 7"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM P at hour 7"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM A at hour 8"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM C at hour 8"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							
estimate "LSM P at hour 8"	intercept 1 basefev1 2.6493 Drug*Hour 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0							



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## PROC BGLIMM Statements – Regression Model

Unequal Slope over Hour by Drug – Test Regression Coefficients

```
data fev1uni; set fev1uni;
   H=hour;
proc bglimm data=fev1uni nmc=10000 seed=44672057
            plots=(trace autocorr density) diagnostics=all;
   class Drug Patient Hour;
   model FEV1 = BaseFev1 drug H(drug);
   random int / subject=Patient;
   repeated Hour / subject=Patient(Drug) type=ar(1) r rcorr;
   estimate "intercept - Drug A" intercept 1 drug 1 0 0;
   estimate "intercept - Drug C" intercept 1 drug 0 1 0;
   estimate "intercept - Drug P" intercept 1 drug 0 0 1;
   estimate "slope - Drug A" H(drug) 1 0 0;
   estimate "slope - Drug C" H(drug) 0 1 0;
   estimate "slope - Drug P" H(drug) 0 0 1;
   estimate "intercept A vs C" drug 1 -1 0;
   estimate "intercept A vs P" drug 1 0 -1;
   estimate "intercept C vs P" drug 0 1 -1;
   estimate "slope A vs C" H(drug) 1 -1 0;
   estimate "slope A vs P" H(drug) 1 0 -1;
   estimate "slope C vs P" H(drug) 0 1 -1;
run;
```



# Results

#### **Effects Model**

Simple Effect Diffs

Results f	rom ES <sup>-</sup>	TIMATE Sta	atements	
		Standard	95% HPD	
Label	Mean	<b>Deviation</b>	Interval	
LSM A at hour 1	3.4735	0.1400	3.1911 3.73	370
LSM C at hour 1	3.6820	0.1387	3.4068 3.95	512
LSM P at hour 1	2.8178	0.1395	2.5410 3.08	89
LSM A at hour 2	3.3965	0.1405	3.1281 3.67	'90
LSM C at hour 2	3.6183	0.1382	3.3483 3.89	947
LSM P at hour 2	2.8828	0.1397	2.6099 3.15	591
LSM A at hour 3	3.1841	0.1405	2.9071 3.45	686
LSM C at hour 3	3.5692	0.1394	3.2962 3.84	84
LSM P at hour 3	2.8891	0.1401	2.6033 3.15	555
LSM A at hour 4	3.0464	0.1411	2.7666 3.32	261
LSM C at hour 4	3.4350	0.1396	3.1570 3.70	070
LSM P at hour 4	2.8619	0.1402	2.5855 3.13	573
LSM A at hour 5	3.0533	0.1415	2.7816 3.33	98
LSM C at hour 5	3.2415	0.1386	2.9692 3.51	31
LSM P at hour 5	2.7595	0.1406	2.4729 3.02	256
LSM A at hour 6	2.9797	0.1411	2.6956 3.24	89
LSM C at hour 6	3.0773	0.1386	2.8061 3.34	93
LSM P at hour 6	2.8064	0.1416	2.5306 3.09	07
LSM A at hour 7	2.8691	0.1403	2.5996 3.15	529
LSM C at hour 7	2.9692	0.1385	2.6919 3.23	316
LSM P at hour 7	2.7755	0.1412	2.4912 3.04	58
LSM A at hour 8	2.8581	0.1395	2.5712 3.11	75
LSM C at hour 8	3.0026	0.1384	2.7331 3.27	'43
LSM P at hour 8	2.7227	0.1403	2.4497 2.99	61

LSMeans

Results from ESTIMATE Statements								
		Standard	95% H	IPD				
Label	Mean	Deviation	Inter	val				
A vs P at hour 1	0.6557	0.0981	0.4626	0.8460				
C vs P at hour 1	0.8642	0.0973	0.6796	1.0579				
A vs P at hour 2	0.5137	0.0969	0.3281	0.7036				
C vs P at hour 2	0.7355	0.0966	0.5482	0.9279				
A vs P at hour 3	0.2950	0.0962	0.1058	0.4832				
C vs P at hour 3	0.6801	0.0968	0.4904	0.8731				
A vs P at hour 4	0.1845	0.0968	-0.00386	0.3702				
C vs P at hour 4	0.5731	0.0969	0.3911	0.7720				
A vs P at hour 5	0.2937	0.0966	0.1056	0.4811				
C vs P at hour 5	0.4819	0.0968	0.2888	0.6659				
A vs P at hour 6	0.1733	0.0973	-0.00990	0.3699				
C vs P at hour 6	0.2709	0.0973	0.0882	0.4660				
A vs P at hour 7	0.0935	0.0966	-0.0891	0.2908				
C vs P at hour 7	0.1937	0.0974	0.00599	0.3858				
A vs P at hour 8	0.1354	0.0971	-0.0530	0.3226				
C vs P at hour 8	0.2799	0.0970	0.0866	0.4702				



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#### Results Regression Model

Posterior Summaries and Intervals				Results fi	rom EST	<b>MATE Stat</b>	ements			
			Standard	95%	HPD			Standard	95%	HPD
Parameter	Ν	Mean	Deviation	Inte	erval	Label	Mean	Deviation	Inte	rval
Intercept	10000	1.4196	0.4008	0.6234	2.1897	intercept - Drug A	2.0774	0.4056	1.2770	2.8641
basefev1	10000	0.5460	0.1419	0.2685	0.8240	intercept - Drug C	2.3473	0.4021	1.5223	3.0958
drug a	10000	0.6577	0.1051	0.4435	0.8524	intercept - Drug P	1.4196	0.4008	0.6234	2.1897
drug c	10000	0.9276	0.1046	0.7222	1.1296	slope - Drug A	-0.0886	0.0135	-0.1148	-0.0619
drug p	0					slope - Drug C	-0.1034	0.0133	-0.1290	-0.0768
H*drug a	10000	-0.0886	0.0135	-0.1148	-0.0619	slope - Drug P	-0.0151	0.0133	-0.0424	0.00932
H*drug c	10000	-0.1034	0.0133	-0.1290	-0.0768	intercept A vs C	-0.2699	0.1071	-0.4790	-0.0588
H*drug p	10000	-0.0151	0.0133	-0.0424	0.00932	intercept A vs P	0.6577	0.1051	0.4435	0.8524
Residual Var	10000	0.1142	0.0119	0.0924	0.1384	intercept C vs P	0.9276	0.1046	0.7222	1.1296
Residual AR(1)	10000	0.6550	0.0356	0.5863	0.7274	slope A vs C	0.0147	0.0189	-0.0235	0.0503
Random Var	10000	0.3506	0.1101	0.1787	0.5748	slope A vs P	-0.0735	0.0189	-0.1095	-0.0356
						slope C vs P	-0.0883	0.0187	-0.1272	-0.0536



# Final Thoughts

PROC GLIMMIX ↔ PROC BGLIMM ↔ PROC MCMC

#### PROC BGLIMM can implement same models as GLIMMIX

- more diagnostics (trace plots, ESS. dependence factor, etc.)
- NBI, NMC, THIN and prior options usually need attention
- OUTPOST & ODS OUTPUT instead of ILINK

#### PROC MCMC

#SASGF

- offers more flexible specification of prior distributions
- e.g. prior centered at fixed effect starting value
- can fit non-linear and semi-parametric mixed models
- allows non-Gaussian random effects
- e.g. Beta-binomial, Poisson-gamma mixed models

# Thank you!

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