A Model Family for Hierarchical Data With Combined Normal and Conjugate Random Effects

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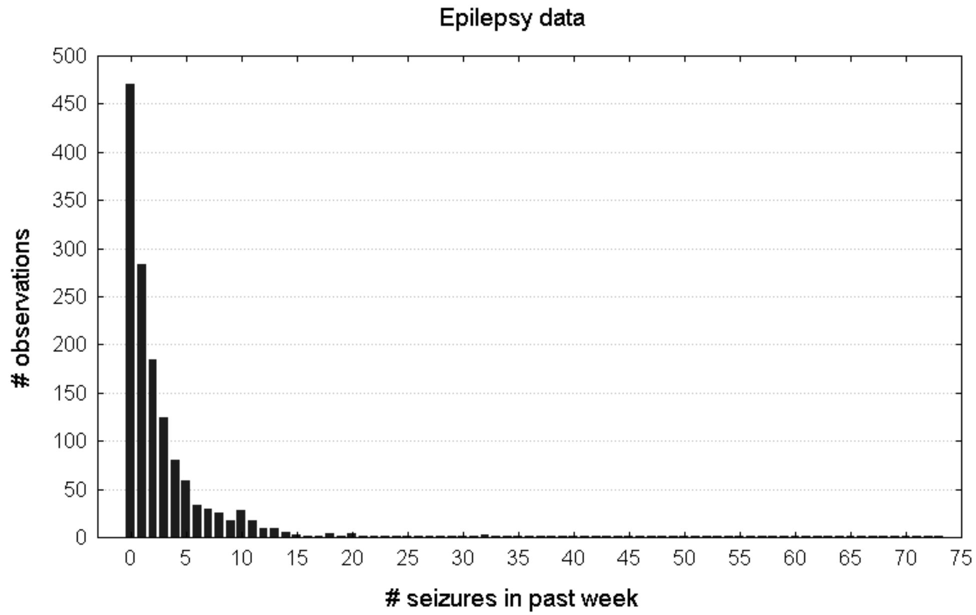
The Epilepsy Data

- Randomized, double-blind, parallel group multi-center study
- placebo (45) $\longleftrightarrow$ new anti-epileptic drug (AED; 44), in combination with other AED's
- 12-week run-in period (baseline period, for stabilization of the use of AED's)
- 16 weeks of follow up (some until week 27)
- outcome of interest: number of epileptic seizures experienced during the last week
- research question: reduction in # seizures by new therapy
- Considerations: longitudinal count data with presence of extreme values, and very few observations available at some of the time-points, especially past week 20

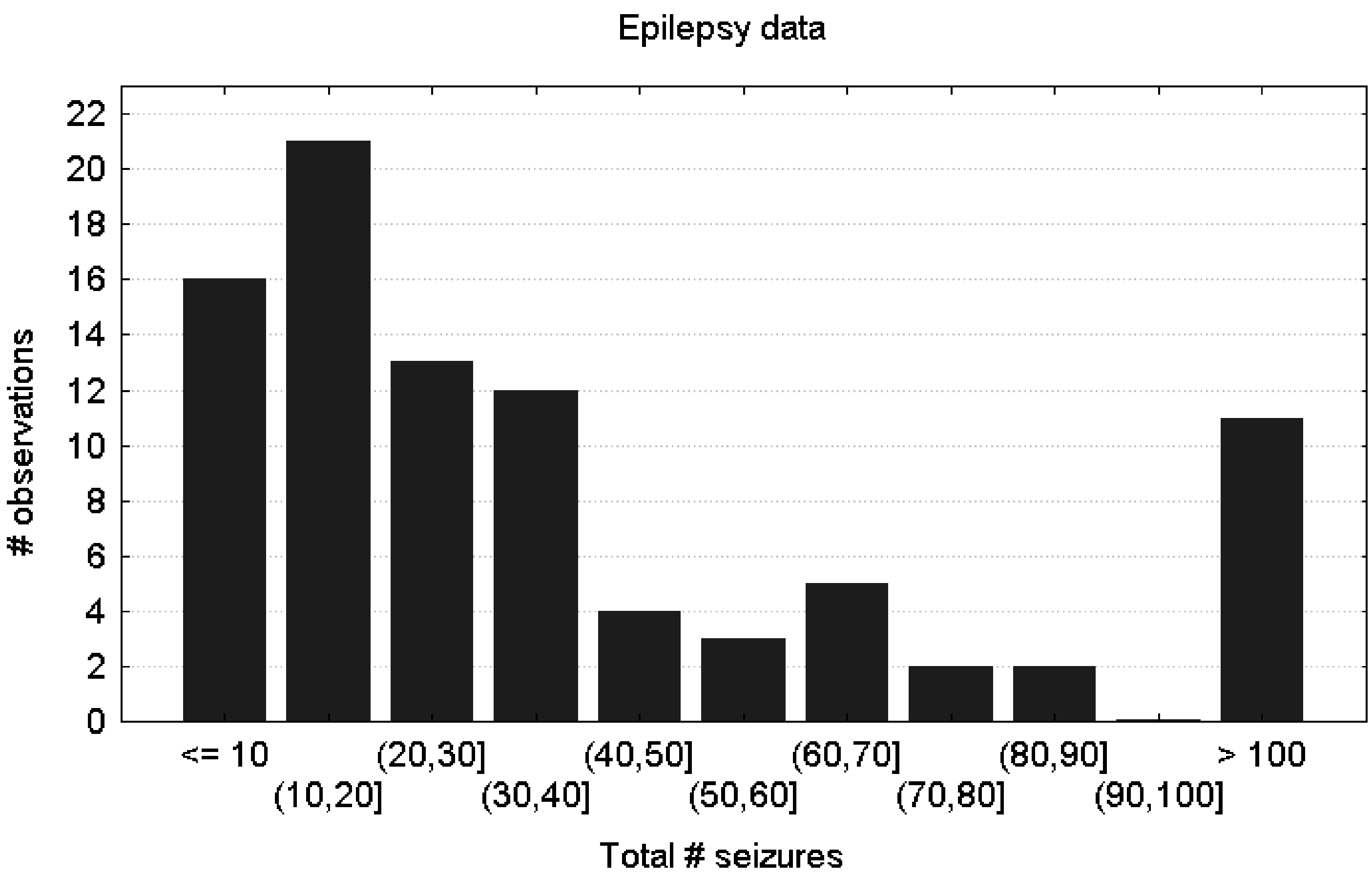


- Let Y_i now be the total number of seizures for subject i:

$$Y_i = \sum_{i=1}^{n_i} Y_{ij}$$

where Y_{ij} was the original (longitudinally measured) weekly outcome.

- Histogram:


Epilepsy data
22
20
18
16
14
12
10
8
6
4
2
0
observations
<= 10
(10,20]
(20,30]
(30,40]
(40,50]
(50,60]
(60,70]
(70,80]
(80,90]
(90,100]
> 100
Total # seizures

- Number of measurements at some time points (very unbalanced):

	# Observations		
Week	Placebo	Treatment	Total
1	45	44	89
5	42	42	84
10	41	40	81
15	40	38	78
16	40	37	77
17	18	17	35
20	2	8	10
27	0	3	3

- As these sums are not taken over an equal number of visits for all subjects, the above histogram is not a 'fair' one as it does not account for differences in n_i for this.

- We will therefore use the following Poisson model:

$$Y_i \sim \text{Poisson}(\lambda_i)$$

$$\ln(\lambda_i / n_i) = \boldsymbol{x_i}'\boldsymbol{\beta}$$

- The regression model is equivalent to

$$\lambda_i = n_i \exp(\boldsymbol{x_i}'\boldsymbol{\beta}) = \exp(\boldsymbol{x_i}'\boldsymbol{\beta} + \ln n_i)$$

- Since n_i is the number of weeks for which the number of seizures was recorded for subject i, $\exp(\boldsymbol{x_i}'\boldsymbol{\beta})$ is the average number of seizures per week

- $\ln n_i$ is called an offset in the above model

- Covariates in $\boldsymbol{x_i}$: treatment & baseline seizure rate

Onychomycosis (Toenail) Data

De Backer, De Keyser, De Vroey, Lesaffre (British Journal of Dermatology 1996)

- **T**oenail **D**ermatophyte **O**nychomycosis: Common toenail infection, difficult to treat
- Classical treatments administered until the whole nail has grown out healthy
- New compounds have been developed that reduce treatment to 3 months
- Randomized, double-blind, parallel group multicenter study for the comparison of two such new compounds (A and B) for oral treatment

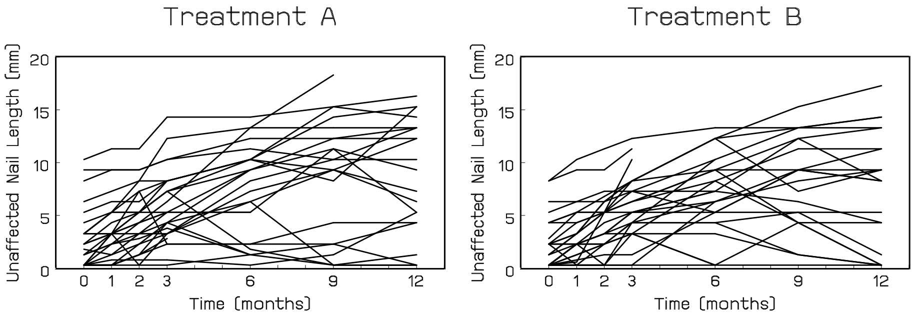
- Design:
  - ▷ 2×189 patients randomized, 36 centers
  - ▷ 48 weeks of total follow up (12 months)
  - ▷ 12 weeks of treatment (3 months)
  - ▷ Measurements at months 0, 1, 2, 3, 6, 9, 12

- Research question:

> Are both treatments equally effective for the treatment of TDO?

Unaffected nail length (mm)?

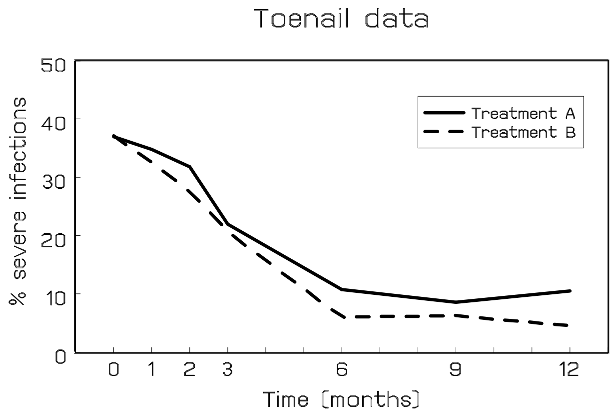
- As response is related to toe size, we restrict to patients with big toenail as target nail $\Longrightarrow$ 150 and 148 subjects
- 30 randomly selected profiles, in each group:



Complication: Dropout (24%):

Severity relative to treatment of TDO?

- coded as 0 (not severe) or 1 (severe)
- Question: Did the percentage of severe infections decrease over time and was the evolution different over time for the two treatments?



Recurrent Asthma Attacks in Children

Duchateau and Janssen (2007)

- Asthma is occurring more frequently in very young children (6–24 months)
- **Prevention trial:** New application of existing anti-allergic drug for high-risk children
- placebo $\longleftrightarrow$ drug
- Usually more than one event $\longrightarrow$ recorded in a diary
- Recorded:
  - ▷ Start and end of risk period
  - ▷ Occurrence of asthma event

Methodological Context

Study type	Outcome type			
	$N(\mu, \sigma^2)$		~~$N(\mu, \sigma^2)$~~	
	Effect	**Param**	**Effect**	**Param**
Y_i	Mean	μ	Mean	μ
	Var.	σ^2	Var.	$\mu \quad (\& \quad \theta_i)$
	Corr.	—	Corr.	(θ_i)
	Effect	**Param**	**Effect**	**Param**
$(Y_{i1}, \ldots, Y_{in_i})$	Mean	$\boldsymbol{\mu}_i$	Mean	$\boldsymbol{\mu}_i$
	Var.	$\boldsymbol{b}_i \quad \& \quad \Sigma_i$	Var.	$\boldsymbol{b}_i \quad (\& \quad \boldsymbol{\theta}_i)$
	Corr.	$\boldsymbol{b}_i \quad \& \quad \Sigma_i$	Corr.	$\boldsymbol{b}_i \quad (\& \quad \boldsymbol{\theta}_i)$

The Generalized Linear Model

- Suppose a sample $Y_1, \dots, Y_N$ of independent observations is available
- All Y_i have densities $f(y_i|\theta_i, \phi)$ which belong to the exponential family:

$$f(y|\theta_i, \phi) = \exp\left\{\phi^{-1}[y\theta_i - \psi(\theta_i)] + c(y, \phi)\right\}$$

- θ_i the natural parameter
- Linear predictor: $\theta_i \;=\; \boldsymbol{x_i}'\boldsymbol{\beta}$
- ϕ is the scale parameter (overdispersion parameter)
- Mean–variance relationship:

$$\text{Var}(Y) \;=\; \phi\psi''\left[\psi'^{-1}(\mu)\right] \;=\; \phi v(\mu)$$

- The function $v(\mu)$ is called the variance function.

- The function ψ'^{-1} which expresses θ as function of μ is called the link function.

- ψ' is *the inverse link function*

Example: The Normal Model

- Model:

$$Y \sim N(\mu, \sigma^2)$$

- Density function:

$$f(y|\theta,\phi) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{-\frac{1}{\sigma^2}(y-\mu)^2\right\}$$

$$= \exp\left\{\frac{1}{\sigma^2}\left(y\mu - \frac{\mu^2}{2}\right) + \left(\frac{\ln(2\pi\sigma^2)}{2} - \frac{y^2}{2\sigma^2}\right)\right\}$$

- Exponential family:
  - ▷ $\theta = \mu$
  - ▷ $\phi = \sigma^2$
  - ▷ $\psi(\theta) = \theta^2/2$
  - ▷ $c(y, \phi) = \frac{\ln(2\pi\phi)}{2} - \frac{y^2}{2\phi}$
- Mean and variance function:
  - ▷ $\mu = \theta$
  - ▷ $v(\mu) = 1$
- Note that, under this normal model, the mean and variance are not related:

$$\phi v(\mu) \;=\; \sigma^2$$

- The link function is here the identity function: $\theta = \mu$

Example: The Bernoulli Model

- Model:

$$Y \sim \text{Bernoulli}(\pi)$$

- Density function:

$$\begin{aligned} f(y|\theta,\phi) &= \pi^y(1-\pi)^{1-y} \\ &= \exp\{y \ln \pi + (1-y)\ln(1-\pi)\} \\ &= \exp\left\{y \ln\left(\frac{\pi}{1-\pi}\right) + \ln(1-\pi)\right\} \end{aligned}$$

- Exponential family:
  - ▷ $\theta = \ln\left(\frac{\pi}{1-\pi}\right)$
  - ▷ $\phi = 1$
  - ▷ $\psi(\theta) = \ln(1-\pi) = \ln(1+\exp(\theta))$
  - ▷ $c(y,\phi) = 0$

- Mean and variance function:
  - ▷ $\mu = \frac{\exp\theta}{1+\exp\theta} = \pi$
  - ▷ $v(\mu) = \frac{\exp\theta}{(1+\exp\theta)^2} = \pi(1-\pi)$

- Note that, under this model, the mean and variance are related:

$$\phi v(\mu) \;=\; \mu(1-\mu)$$

- The link function here is the logit link: $\theta = \ln\left(\frac{\mu}{1-\mu}\right)$

Example: The Poisson Model

- Model:

$$Y \sim \text{Poisson}(\lambda)$$

- Density function:

$$\begin{aligned} f(y|\theta, \phi) &= \frac{e^{-\lambda}\lambda^y}{y!} \\ &= \exp\{y \ln \lambda - \lambda - \ln y!\} \end{aligned}$$

- Exponential family:
  - ▷ $\theta = \ln \lambda$
  - ▷ $\phi = 1$
  - ▷ $\psi(\theta) = \lambda = \exp \theta$
  - ▷ $c(y, \phi) = -\ln y!$
- Mean and variance function:
  - ▷ $\mu = \exp \theta = \lambda$
  - ▷ $v(\mu) = \exp \theta = \lambda$
- Note that, under this model, the mean and variance are related:

$$\phi v(\mu) = \mu$$

- The link function is here the log link: $\theta = \ln \mu$

Standard Overdispersion Models

- $\phi \neq 1 \qquad \Longrightarrow \qquad \mathsf{Var}(Y_i) = \phi\mu_i$

- **Two-stage approach:**

  ▷ Formulation:

$$\begin{aligned} Y_i|\lambda_i &\sim \mathsf{Poi}(\lambda_i) \\ \mathsf{E}(\lambda_i) &= \mu_i \\ \mathsf{Var}(\lambda_i) &= \sigma_i^2 \end{aligned}$$

  ▷ Implications:

$$\begin{aligned} \mathsf{E}(Y_i) &= \mathsf{E}[\mathsf{E}(Y_i|\lambda_i)] = \mathsf{E}(\lambda_i) = \mu_i \\ \mathrm{Var}(Y_i) &= \mathsf{E}[\mathrm{Var}(Y_i|\lambda_i)] + \mathrm{Var}[\mathsf{E}(Y_i|\lambda_i)] = \mathsf{E}(\lambda_i) + \mathrm{Var}(\lambda_i) = \mu_i + \sigma_i^2 \end{aligned}$$

- **Repeated-measures version:**

$$\begin{aligned}
\boldsymbol{\lambda}_i &= (\lambda_{i1}, \ldots, \lambda_{in_i})' \\
\mathsf{E}(\boldsymbol{\lambda}_i) &= \boldsymbol{\mu}_i \\
\mathrm{Var}(\boldsymbol{\lambda}_i) &= \boldsymbol{\Sigma}_i \\
\mathsf{E}(\boldsymbol{Y_i}) &= \boldsymbol{\mu}_i \\
\mathrm{Var}(\boldsymbol{Y_i}) &= M_i + \Sigma_i
\end{aligned}$$

The Standard Poisson-normal Model

- **General formulation:**

$$
\begin{aligned}
f_i(y_{ij}|\boldsymbol{b_i}, \boldsymbol{\beta}, \phi) &= \exp\{\phi^{-1}[y_{ij}\theta_{ij} - \psi(\theta_{ij})] + c(y_{ij}, \phi)\} \\
\eta(\mu_{ij}) &= \eta[E(Y_{ij}|\boldsymbol{b_i})] = \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{b_i} \\
\boldsymbol{b_i} &\sim N(\mathbf{0}, D)
\end{aligned}
$$

- **Poisson formulation:**

$$
\begin{aligned}
Y_{ij} &\sim \mathsf{Poi}(\lambda_{ij}) \\
\ln(\lambda_{ij}) &= \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{b_i} \\
\boldsymbol{b_i} &\sim N(\mathbf{0}, D)
\end{aligned}
$$

- **Marginal moments:**

$$\mu_{ij} = \exp\left(\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \frac{1}{2}\boldsymbol{z}'_{ij}D\boldsymbol{z}_{ij}\right)$$

$$\text{Var}(\boldsymbol{Y_i}) = M_i + M_i\left(e^{Z_iDZ'_i} - J_{n_i}\right)M_i$$

- **Univariate version of the marginal moments:**

$$\mu_i = \exp\left(x'_i\boldsymbol{\beta} + \frac{1}{2}d\right)$$

$$\text{Var}(Y_i) = \mu_i + \mu_i^2(e^d - 1)$$

A Combined Model: The Poisson-(. . .)-normal Model

- **Model formulation:**

$$\begin{aligned}
Y_{ij} &\sim \text{Poi}(\lambda_{ij}) \\
\lambda_{ij} &= \theta_{ij} \exp\left(\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{b_i}\right) \\
\boldsymbol{b_i} &\sim N(\mathbf{0}, D) \\
\mathsf{E}(\boldsymbol{\theta}_i) = \mathsf{E}[(\theta_{i1}, \ldots, \theta_{in_i})'] &= \Phi_i \quad \text{and} \quad \text{Var}(\boldsymbol{\theta}_i) = \Sigma_i
\end{aligned}$$

- **Marginal moments:**

$$\mu_{ij} = \phi_{ij} \exp\left(\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \frac{1}{2}\boldsymbol{z}'_{ij}D\boldsymbol{z}_{ij}\right)$$

$$\mathrm{Var}(\boldsymbol{Y_i}) = M_i + M_i\left(P_i - J_{n_i}\right)M_i$$

$$p_{i,jk} = \exp\left(\frac{1}{2}\boldsymbol{z}'_{ij}Dz_{ik}\right) \cdot \frac{\sigma_{i,jk} + \phi_{ij}\phi_{ik}}{\phi_{ij}\phi_{ik}} \cdot \exp\left(\frac{1}{2}z'_{ik}D\boldsymbol{z}_{ij}\right)$$

- **Univariate version of the marginal moments:**

$$\mu_i = \phi_i \exp\left(x'_i\boldsymbol{\beta} + \frac{1}{2}d\right)$$

$$\mathrm{Var}(Y_i) = \mu_i + \mu_i^2 \cdot \left(e^d - 1 + \frac{\sigma_i^2}{\phi_i^2}e^d\right)$$

Fully Parametric Specification

- So far, random effects are specified only in a moment-based fashion:
  - ▷ Mean
  - ▷ Variance
- Fully parametric specification is possible
- Gamma specification is sensible
- Univariate case: **the negative-binomial model**
- Hierarchical case: **the Poisson-gamma-normal model**

The Negative-binomial Model

$$\lambda \sim \text{Gamma}(\alpha, \beta)$$

$$f(\lambda) = \frac{1}{\beta^\alpha \Gamma(\alpha)} \lambda^{\alpha-1} e^{-\lambda/\beta}$$

$$\text{P}(Y = y) = \frac{1}{\beta^\alpha \Gamma(\alpha)} \int_0^{+\infty} \lambda^{\alpha-1} e^{-\lambda/\beta} \frac{\lambda^y e^{-\lambda}}{y!}$$

$$= \binom{\alpha + y - 1}{\alpha - 1} \left(\frac{\beta}{\beta + 1}\right)^y \left(\frac{1}{\beta}\right)^\alpha$$

The Poisson-gamma-normal Model

- **The marginal probability mass function:**

$$\mathsf{P}(\boldsymbol{Y_i} = \boldsymbol{y_i}) = \sum_{\boldsymbol{t}} \left[\prod_{j=1}^{n_i} \begin{pmatrix} y_{ij} + t_j \\ y_{ij} \end{pmatrix} \cdot \begin{pmatrix} \alpha_j + y_{ij} + t_j - 1 \\ \alpha_j - 1 \end{pmatrix} \cdot (-1)^{t_j} \cdot \beta_j^{y_{ij}+t_j} \right]$$

$$\times \exp\left(\sum_{j=1}^{n_i} (y_{ij} + t_j) \boldsymbol{x}'_{ij} \boldsymbol{\beta} \right) \times \exp\left\{ \frac{1}{2} \left[\sum_{j=1}^{n_i} (y_{ij} + t_j) \boldsymbol{z}'_{ij} \right] D \left[\sum_{j=1}^{n_i} (y_{ij} + t_j) \boldsymbol{z}_{ij} \right] \right\}$$

- **The special case of the Poisson-normal model:**

$$\mathsf{P}(\boldsymbol{Y_i} = \boldsymbol{y_i}) = \frac{1}{\Pi_{j=1}^{n_i} y_{ij}!} \sum_{\boldsymbol{t}} \frac{(-1)^{\Sigma_{j=1}^{n_i} t_j}}{\Pi_{j=1}^{n_i} t_j!} \cdot \exp\left[\sum_{j=1}^{n_i} (y_{ij} + t_j) \boldsymbol{x}'_{ij} \boldsymbol{\beta} \right]$$

$$\times \exp\left\{ \frac{1}{2} \left[\sum_{j=1}^{n_i} (y_{ij} + t_j) \boldsymbol{z}'_{ij} \right] D \left[\sum_{j=1}^{n_i} (y_{ij} + t_j) \boldsymbol{z}_{ij} \right] \right\}$$

- **Univariate case for Poisson-gamma-normal model:**

$$\mathsf{P}(Y_i = y_i) = \sum_{t=0}^{+\infty} \binom{y_i + t}{y_i} \binom{\alpha + y_i + t - 1}{\alpha - 1} \beta^{y_i+t} (-1)^t \exp\left[x_i' \boldsymbol{\beta}(y_i + t) + \frac{1}{2} d (y_i + t)^2\right]$$

- **Univariate case for Poisson-normal model:**

$$\mathsf{P}(Y_i = y_i) = \frac{1}{y_i!} \sum_{t=0}^{+\infty} \frac{(-1)^t}{t!} \exp\left[x_i' \boldsymbol{\beta}(y_i + t) + \frac{1}{2} d (y_i + t)^2\right]$$

Estimation

- Integrate over the gamma random effects **only**:

$$\mathsf{P}(Y_{ij} = y_{ij}|\boldsymbol{b_i}) \;=\; \begin{pmatrix} \alpha_j + y_{ij} - 1 \\ \\ \alpha_j - 1 \end{pmatrix} \cdot \left(\frac{\beta_j}{1+\kappa_{ij}\beta_j}\right)^{y_{ij}} \cdot \left(\frac{1}{1+\kappa_{ij}\beta_j}\right)^{\alpha_j} \kappa_{ij}^{y_{ij}}$$

$$\kappa_{ij} \;=\; \exp[\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{b_i}]$$

- Can be fitted using the SAS procedure NLMIXED

- Model for the epilepsy data:

$$\ln(\lambda_{ij}) \;=\; \begin{cases} (\beta_{00} + b_i) + \beta_{01} t_{ij} & \text{if placebo} \\ \\ (\beta_{10} + b_i) + \beta_{11} t_{ij} & \text{if treated,} \end{cases}$$

$$b_i \;\sim\; N(0, d)$$

SAS Code: Poisson-normal Model

```
proc nlmixed data=test qpoints=50;
title 'Poisson-normal Model';
parms int0=0.5 slope0=-0.1 int1=1 slope1=0.1 sigma=1;
if (trt = 0) then eta = int0 + b + slope0*time;
else if (trt = 1) then eta = int1 + b + slope1*time;
lambda = exp(eta);
model nseizw ~ poisson(lambda);
random b ~ normal(0,sigma**2) subject = id;
estimate 'difference in slope' slope1-slope0;
estimate 'ratio of slopes' slope1/slope0;
estimate 'variance RIs' sigma**2;
run;
```

SAS Code: Poisson-gamma-normal Model

```
proc nlmixed data=test qpoints=50;
title 'Poisson-Combined Model';
parms int0=0.5 slope0=-0.1 int1=1 slope1=0.1 sigma=1 alpha=5;
if (trt = 0) then eta = int0 + b + slope0*time;
else if (trt = 1) then eta = int1 + b + slope1*time;
lambda = exp(eta);
beta=1;
loglik=lgamma(alpha+y)-lgamma(alpha)+y*log(beta)
       -(y+alpha)*log(1+beta*lambda+y*eta;
model y ~ general(loglik);
random b ~ normal(0,sigma**2) subject = id;
estimate 'difference in slope' slope1-slope0;
estimate 'ratio of slopes' slope1/slope0;
estimate 'variance RIs' sigma**2;
run;
```

The Epilepsy Data

Effect	Parameter	Poisson Estimate (s.e.)	Negative-binomial Estimate (s.e.)
Intercept placebo	β_{00}	1.2662 (0.0424)	1.2594 (0.1119)
Slope placebo	β_{01}	-0.0134 (0.0043)	-0.0126 (0.0111)
Intercept treatment	β_{10}	1.4531 (0.0383)	1.4750 (0.1093)
Slope treatment	β_{11}	-0.0328 (0.0038)	-0.0352 (0.0101)
Negative-binomial parameter	α_1	—	0.5274 (0.0255)
Negative-binomial parameter	$\alpha_2 = 1/\alpha_1$	—	1.8961 (0.0918)
Variance of random intercepts	d	—	—

Effect	Parameter	Poisson-normal Estimate (s.e.)	Combined Estimate (s.e.)
Intercept placebo	β_0	0.8179 (0.1677)	0.9112 (0.1755)
Slope placebo	β_1	-0.0143 (0.0044)	-0.0248 (0.0077)
Intercept treatment	β_0	0.6475 (0.1701)	0.6555 (0.1782)
Slope treatment	β_2	-0.0120 (0.0043)	-0.0118 (0.0074)
Negative-binomial parameter	α_1	—	2.4640 (0.2113)
Negative-binomial parameter	$\alpha_2 = 1/\alpha_1$	—	0.4059 (0.0348)
Variance of random intercepts	d	1.1568 (0.1844)	1.1289 (0.1850)

Implications for Correlation Function

		Smallest value		Largest value	
Model	Arm	ρ	time pair	ρ	time pair
Poisson-normal	placebo	0.8577	26 & 27	0.8960	1 & 2
Poisson-normal	treatment	0.8438	26 & 27	0.8794	1 & 2
Combined	placebo	0.3041	26 & 27	0.3134	1 & 2
Combined	treatment	0.2234	1 & 2	0.3410	26 & 27

Implications for Hypothesis Testing

	p-**values**	
Model	$H_0 : \beta_{11} - \beta_{01} = 0$	$H_0 : \beta_{11}/\beta_{01} = 1$
Poisson	**0.0008**	**0.0038**
Poisson-normal	0.7115	**0.0376**
negative-binomial	**0.0131**	0.2815
combined	0.2260	0.1591

The General Case

$$
\begin{aligned}
f_i(y_{ij}|\boldsymbol{b_i},\boldsymbol{\xi}) &= \exp\left\{\phi^{-1}[y_{ij}\lambda_{ij}-\psi(\lambda_{ij})]+c(y_{ij},\phi)\right\} \\
E(Y_{ij}|\theta_{ij},\boldsymbol{b_i}) &= \mu_{ij}^c = \theta_{ij}\kappa_{ij} \\
\theta_{ij} &\sim \mathcal{G}_{ij}(\xi_{ij},\sigma_{ij}^2) \\
\kappa_{ij} &= g(\boldsymbol{x}_{ij}'\boldsymbol{\xi}+\boldsymbol{z}_{ij}'\boldsymbol{b_i}) \\
\boldsymbol{b_i} &\sim N(\mathbf{0},D) \\
\eta_{ij} &= \boldsymbol{x}_{ij}'\boldsymbol{\xi}+\boldsymbol{z}_{ij}'\boldsymbol{b_i}
\end{aligned}
$$

Classical Conjugacy

$$f(y|\theta) = \exp\{\phi^{-1}[yh(\theta) - g(\theta)] + c(y,\phi)\}$$

$$f(\theta) = \exp\{\gamma[\psi h(\theta) - g(\theta)] + c^*(\gamma,\psi)\}$$

$$f(y) = \exp\left[c(y,\phi) + c^*(\gamma,\psi) - c^*\left(\phi^{-1} + \gamma, \frac{\phi^{-1}y + \gamma\psi}{\phi^{-1} + \gamma}\right)\right]$$

Strong Conjugacy

- Write:

$$f(y|\kappa\theta) = \exp\left\{\phi^{-1}[yh(\kappa\theta) - g(\kappa\theta)] + c(y,\phi)\right\}$$

- Apply the transformation theorem:

$$f(\theta|\gamma,\psi) = \kappa \cdot f(\kappa\theta|\widetilde{\gamma},\widetilde{\psi})$$

- Request the form:

$$f(\kappa\theta) = \exp\left\{\gamma^*[\psi^* h(\kappa\theta) - g(\kappa\theta)] + c^{**}(\gamma^*,\psi^*)\right\}$$

- Leading to the marginal model:

$$f(y|\kappa) = \exp\left\{c(y,\phi) + c^{**}(\gamma^*,\psi^*) + c^{**}\left(\phi^{-1} + \gamma^*, \frac{\phi^{-1}y + \gamma^*\psi^*}{\phi^{-1} + \gamma^*}\right)\right\}$$

The Weibull Case

- **The Weibull-gamma-normal model:**

$$f(\boldsymbol{y}_i|\boldsymbol{\theta}_i,\boldsymbol{b_i}) \;=\; \prod_{j=1}^{n_i} \lambda\rho\theta_{ij}y_{ij}^{\rho-1}e^{\boldsymbol{x}'_{ij}\boldsymbol{\beta}+\boldsymbol{z}'_{ij}\boldsymbol{b_i}}e^{-\lambda y_{ij}^{\rho}\theta_{ij}e^{\boldsymbol{x}'_{ij}\boldsymbol{\beta}+\boldsymbol{z}'_{ij}\boldsymbol{b_i}}}$$

$$f(\boldsymbol{\theta}_i) \;=\; \prod_{j=1}^{n_i} \frac{1}{\beta_j^{\alpha_j}\Gamma(\alpha_j)}\theta_{ij}^{\alpha_j-1}e^{-\theta_{ij}/\beta_j}$$

$$f(\boldsymbol{b_i}) \;=\; \frac{1}{(2\pi)^{q/2}|D|^{1/2}}e^{-\frac{1}{2}\boldsymbol{b_i}'D^{-1}\boldsymbol{b_i}}$$

- **Closed forms for marginal density and marginal moments**

- **Marginal density:**

$$f(\boldsymbol{y}_i) = \sum_{(m_1,\dots,m_{n_i})} \prod_{j=1}^{n_i} \frac{(-1)^{m_j}}{m_j!} \frac{\Gamma(\alpha_j + m_j + 1)\beta_j^{m_j+1}}{\Gamma(\alpha_j)} \lambda^{m_j+1} \rho y_{ij}^{(m_j+1)\rho-1}$$
$$\times \exp\left\{(m_j+1)\left[\boldsymbol{x}_{ij}'\boldsymbol{\beta} + \frac{1}{2}(m_j+1)\cdot \boldsymbol{z}_{ij}' D \boldsymbol{z}_{ij}\right]\right\}$$

- **Marginal moments:**

$$E(Y_{ij}^k) = \frac{\alpha_j B(\alpha_j - k/\rho, k/\rho + 1)}{\lambda^{k/\rho}\beta_j^{k/\rho}} \exp\left(-\frac{k}{\rho}\boldsymbol{x}_{ij}'\boldsymbol{\beta} + \frac{k^2}{2\rho^2}\boldsymbol{z}_{ij}' D \boldsymbol{z}_{ij}\right)$$

$$E(Y_{ij}) = \frac{\alpha_j B(\alpha_j - 1/\rho, 1/\rho + 1)}{\lambda^{1/\rho}\beta_j^{1/\rho}} \exp\left(-\frac{1}{\rho}\boldsymbol{x}_{ij}'\boldsymbol{\beta} + \frac{1}{2\rho^2}\boldsymbol{z}_{ij}' D \boldsymbol{z}_{ij}\right)$$

$$\mathsf{Var}(Y_{ij}) = \frac{\alpha_j}{\lambda^{2/\rho}\beta_j^{2\rho}} \exp\left(-\frac{2}{\rho}\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \frac{1}{\rho^2}\boldsymbol{z}'_{ij}D\boldsymbol{z}_{ij}\right)$$

$$\times \left[B\left(\alpha_j - 2/\rho, 2/\rho + 1\right)\exp\left(\frac{1}{\rho^2}\boldsymbol{z}'_{ij}D\boldsymbol{z}_{ij}\right) - \alpha_j B\left(\alpha_j - \frac{1}{\rho}, \frac{1}{\rho} + 1\right)^2\right]$$

$$\mathsf{Cov}(Y_{ij}, Y_{ik}) = \frac{\alpha_j\alpha_k}{\lambda^{2/\rho}\beta_j^{1/\rho}\beta_k^{1/\rho}} \exp\left[-\frac{1}{\rho}(\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{x}'_{ik}\boldsymbol{\beta})\right]$$

$$\times B\left(\alpha_j - \frac{1}{\rho}, \frac{1}{\rho} + 1\right) B\left(\alpha_k - \frac{1}{\rho}, \frac{1}{\rho} + 1\right)$$

$$\times \exp\left[\frac{1}{2\rho^2}(\boldsymbol{z}'_{ij}D\boldsymbol{z}_{ij} + \boldsymbol{z}'_{ik}D\boldsymbol{z}_{ik})\right]\left[\exp\left(\frac{1}{\rho^2}\boldsymbol{z}'_{ij}D\boldsymbol{z}_{ik}\right) - 1\right]$$

- **Identifiability** can be achieved in, for example, two ways:

$$f(\boldsymbol{\theta}_i) = \prod_{j=1}^{n_i} \frac{1}{\left(\frac{1}{\alpha_j}\right)^{\alpha_j} \Gamma(\alpha_j)} \theta_{ij}^{\alpha_j - 1} e^{-\alpha_j \theta_{ij}}$$

$$f(\boldsymbol{\theta}_i) = \prod_{j=1}^{n_i} \delta_j e^{-\delta_j \theta_{ij}}$$

- For the second case:

$$E(Y_{ij}^k) = \frac{\delta_j^{k/\rho} k}{\lambda^k} \Gamma\left(1 - \frac{k}{\rho}\right) \Gamma\left(\frac{k}{\rho}\right) \exp\left(-\frac{k}{\rho} \boldsymbol{x}'_{ij} \boldsymbol{\beta} + \frac{k^2}{2\rho^2} \boldsymbol{z}'_{ij} D \boldsymbol{z}_{ij}\right)$$

- **Weibull** $\longrightarrow$ **Exponential**

$$E(Y_{ij}^k) = \frac{\delta_j^k k}{\lambda^k} \Gamma(1 - k) \Gamma(k) \exp\left(-k \boldsymbol{x}'_{ij} \boldsymbol{\beta} + \frac{k^2}{2} \boldsymbol{z}'_{ij} D \boldsymbol{z}_{ij}\right)$$

- **Univariate case, Weibull-exponential:**

$$f(y) = \frac{\varphi \rho y^{\rho-1}\delta}{(\delta + \varphi y^{\rho})^2}$$

$$E(Y^k) = \frac{k}{\rho}\left(\frac{\delta}{\varphi}\right)^{k\rho} \cdot \Gamma(1 - k/\rho) \cdot \Gamma(k/\rho)$$

- **Univariate case, exponential-exponential:**

$$f(y) = \frac{\varphi\delta}{(\delta + \varphi y)^2}$$

$$E(Y^k) = k\left(\frac{\delta}{\varphi}\right)^{k} \cdot \Gamma(1 - k) \cdot \Gamma(k)$$

- This leads to a class of **“Cauchy-type”** distributions, including the log-logistic distribution, of which there are known to be problems.

- **Estimation using the marginal-conditional approach:**

$$f(y_{ij}|\boldsymbol{b_i}) = \frac{\lambda\kappa_{ij}e^{\mu_{ij}}\rho y_{ij}^{\rho-1}\alpha_j\beta_j}{(1+\lambda\kappa_{ij}e^{\mu_{ij}}\beta_j y_{ij}^{\rho})^{\alpha_j+1}}$$

- **Further issues:**

  ▷ censorship

  ▷ related functions

  ▷ non-parametric baseline hazard functions

Analysis of the Asthma Data

- **Model:**

$$\kappa_{ij} = \xi_0 + b_i + \xi_1 T_i$$

- where

  ▷ T_i: indicator for treatment

  ▷ $b_i \sim N(0, d)$

Effect	Parameter	Exponential Estimate (s.e.)	Exponential-gamma Estimate (s.e.)
Intercept	ξ_0	-3.3709 (0.0772)	-3.9782 (15.354)
Treatment effect	ξ_1	-0.0726 (0.0475)	-0.0755 (0.0605)
Shape parameter	λ	0.8140 (0.0149)	1.0490 (16.106)
Std. dev random effect	$\sqrt{d}$	—	—
Gamma parameter	γ	—	3.3192 (0.3885)
-2log-likelihood		18,693	18,715

Effect	Parameter	Exponential-normal Estimate (s.e.)	Combined Estimate (s.e.)
Intercept	ξ_0	-3.8095 (0.1028)	3.9923 (20.337)
Treatment effect	ξ_1	-0.0825 (0.0731)	-0.0887 (0.0842)
Shape parameter	λ	0.8882 (0.0180)	0.8130 (16.535)
Std. dev random effect	$\sqrt{d}$	0.4097 (0.0386)	0.4720 (0.0416)
Gamma parameter	γ	—	6.8414 (1.7146)
-2log-likelihood		18,611	18,629

The Asthma Data: Wald Tests

Model	Z value	p value
Exponential	-1.5283	0.1264
Exponential-gamma	-1.1293	0.2588
Exponential-normal	-1.2480	0.2120
Combined	-1.0534	0.2921

The Binary Case

- **A logit formulation:**

$$Y_{ij} \sim \text{Bernoulli}(\pi_{ij} = \theta_{ij}\kappa_{ij})$$

$$\kappa_{ij} = \frac{\exp\left(\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{b_i}\right)}{1 + \exp\left(\boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{b_i}\right)}$$

- No closed forms

- Conjugacy $\longrightarrow$ no **strong** conjugacy

- **Marginal-conditional version** (for NLMIXED implementation)

$$f(y_{ij}|\boldsymbol{b_i}) = \frac{1}{\alpha_j + \beta_j} \cdot (\kappa_{ij}\alpha_j)^{y_{ij}} \cdot [(1 - \kappa_{ij})\alpha_j + \beta_j]^{1-y_{ij}}$$

- **A probit formulation** $\longrightarrow$ **closed forms**

- A probit formulation:

$$
\begin{aligned}
\kappa_{ij} &= \Phi_1(\boldsymbol{x}_{ij}'\boldsymbol{\beta} + \boldsymbol{z}_{ij}'\boldsymbol{b_i}) \\
\theta_{ij} &\sim \text{Beta}(\alpha, \beta) \\
f_{n_i}(\boldsymbol{y}_i = \mathbf{1}) &= \left(\frac{\alpha}{\alpha + \beta}\right)^{n_i} \cdot \Phi_{n_i}(X_i\boldsymbol{\beta}; L_{n_i}^{-1}) \\
L_{n_i} &= I_{n_i} - Z_i\left(D^{-1} + Z_i'Z_i\right)^{-1} Z_i' \\
E(Y_{ij}) &= \frac{\alpha}{\alpha + \beta} \cdot \Phi_1(\boldsymbol{x}_{ij}'\boldsymbol{\beta}; L_1^{-1}) = \frac{\alpha}{\alpha + \beta} \cdot \Phi_1(|I + Dz_{ij}z_{ij}'|^{-1/2}\boldsymbol{x}_{ij}'\boldsymbol{\beta}) \\
\text{Var}(Y_{ij}) &= \frac{\alpha}{\alpha + \beta} \cdot \Phi_1(\boldsymbol{x}_{ij}'\boldsymbol{\beta}; L_1^{-1}) \cdot \left[1 - \frac{\alpha}{\alpha + \beta}.\Phi_1(\boldsymbol{x}_{ij}'\boldsymbol{\beta}; L_1^{-1})\right]
\end{aligned}
$$

$$\text{Cov}(Y_{ij}, Y_{ik}) = \left(\frac{\alpha}{\alpha+\beta}\right)^2 \cdot \left\{ \Phi_2 \left[\begin{pmatrix} \boldsymbol{x}'_{ij} \\ \\ \boldsymbol{x}'_{ik} \end{pmatrix} \boldsymbol{\beta}, L_{2jk}^{-1} \right] - \Phi_1(\boldsymbol{x}'_{ij}\boldsymbol{\beta}; L_{1j}^{-1}) \Phi_1(\boldsymbol{x}'_{ik}\boldsymbol{\beta}; L_{1k}^{-1}) \right\}$$

$$L_{2jk} = I_2 - \begin{pmatrix} \boldsymbol{z}'_{ij} \\ \\ \boldsymbol{z}'_{ik} \end{pmatrix} \left[D^{-1} + \begin{pmatrix} \boldsymbol{z}'_{ij} \\ \\ \boldsymbol{z}'_{ik} \end{pmatrix} (\boldsymbol{z}_{ij} \; \boldsymbol{z}_{ik}) \right]^{-1} (\boldsymbol{z}_{ij} \; \boldsymbol{z}_{ik})$$

- The above gives the "success probabilities;" $\longrightarrow$ all other joint probabilities can be derived in a similar fashion

Toenail Data: Unaffected Nail Length

- **Model:**

$$E(Y_{ij}|T_i, t_j, \boldsymbol{\beta}) = \beta_0 + \beta_1 T_i + \beta_2 t_j + \beta_3 T_i t_j$$

- where:

  ▷ Y_{ij}: unaffected nail length for subject i at occasion j

  ▷ t_j: time at which the jth measurement is made

  ▷ T_i: treatment indicator for subject i

Effect	Parameter	Logistic Estimate (s.e.)	Beta-binomial Estimate (s.e.)
Intercept treatment A	ξ_0	−0.5571 (0.1090)	17.9714 (1482.6)
Slope treatment A	ξ_1	−0.1769 (0.0246)	5.2454 (12970.0)
Intercept treatment B	ξ_2	−0.5335 (0.1122)	18.6744 (2077.13)
Slope treatment B	ξ_3	−0.2549 (0.0309)	4.7775 (12912.0)
Std. dev random effect	$\sqrt{d}$	—	—
Ratio	α/β	—	3.6739 (0.2051)
−2log-likelihood		1812	1980

Effect	Parameter	Logistic-normal Estimate (s.e.)	Combined Estimate (s.e.)
Intercept treatment A	ξ_0	−1.6299 (0.4354)	−1.6042 (4.0263)
Slope treatment A	ξ_1	−0.4042 (0.0460)	−6.4783 (1.4386)
Intercept treatment B	ξ_2	−1.7486 (0.4478)	−16.2079 (3.5830)
Slope treatment B	ξ_3	−0.5634 (0.0602)	−8.0745 (1.5997)
Std. dev random effect	$\sqrt{d}$	4.0150 (0.3812)	60.8835 (14.2237)
Ratio	α/β	—	0.2805 (0.0350)
−2log-likelihood		1248	1240

Concluding Table

Element	notation	continuous	binary	count	time to event	
				Standard univariate exponential family		
Model		**normal**	**Bernoulli**	**Poisson**	**Exponential**	**Weibull**
Model	$f(y)$	$\frac{1}{\sigma\sqrt{2\pi}}e^{-\frac{(y-\mu)^2}{2\sigma^2}}$	$\pi^y\,(1-\pi)^{1-y}$	$\frac{e^{-\lambda}\lambda^y}{y!}$	$\varphi e^{-\varphi y}$	$\varphi\rho y^{\rho-1}e^{-\varphi y^\rho}$
Nat. param	η	μ	$\ln\left[\pi/(1-\pi)\right]$	$\ln\lambda$	$-\varphi$	
Mean function	$\psi(\eta)$	$\eta^2/2$	$\ln[1+\exp(\eta)]$	$\lambda=\exp(\eta)$	$-\ln(-\eta)$	
Norm. constant	$c(y,\phi)$	$\frac{\ln(2\pi\phi)}{2}-\frac{y^2}{2\phi}$	0	$-\ln y!$	0	
(Over)dispersion	ϕ	σ^2	1	1	1	
Mean	μ	μ	π	λ	φ^{-1}	$\varphi^{-1/\rho}\Gamma(\rho^{-1}+1)$
Variance	$\phi v(\mu)$	σ^2	$\pi(1-\pi)$	λ	φ^{-2}	$\varphi^{-2/\rho}\left[\Gamma(2\rho^{-1}+1)-\Gamma(\rho^{-1}+1)^2\right]$
				Exponential family with conjugate random effects		
Model		**normal-normal**	**Beta-binomial**	**Negative binomial**	**Exponential-gamma**	**Weibull-gamma**
Hier. model	$f(y\vert\theta)$	$\frac{1}{\sigma\sqrt{2\pi}}e^{-\frac{(y-\theta)^2}{2\sigma^2}}$	$\theta^y\,(1-\theta)^{1-y}$	$\frac{e^{-\theta}\theta^y}{y!}$	$\varphi\theta e^{-\varphi\theta y}$	$\varphi\theta\rho y^{\rho-1}e^{-\varphi\theta y^\rho}$
RE model	$f(\theta)$	$\frac{1}{\sqrt{d}\sqrt{2\pi}}e^{-\frac{(\theta-\mu)^2}{2d}}$	$\frac{\theta^{\alpha-1}(1-\theta)^{\beta-1}}{B(\alpha,\beta)}$	$\frac{\theta^{\alpha-1}e^{-\theta/\beta}}{\beta^\alpha\Gamma(\alpha)}$	$\frac{\theta^{\alpha-1}e^{-\theta/\beta}}{\beta^\alpha\Gamma(\alpha)}$	$\frac{\theta^{\alpha-1}e^{-\theta/\beta}}{\beta^\alpha\Gamma(\alpha)}$
Marg. model	$f(y)$	$\frac{1}{\sqrt{\sigma^2+d}\sqrt{2\pi}}e^{-\frac{(y-\mu)^2}{2(\sigma^2+d)}}$	$(\alpha+\beta)\frac{\Gamma(\alpha)}{\Gamma(\alpha+y)}\frac{\Gamma(\beta)}{\Gamma(\beta+1-y)}$	$\frac{\Gamma(\alpha+y)}{y!\Gamma(\alpha)}\left(\frac{\beta}{\beta+1}\right)^y\left(\frac{1}{\beta+1}\right)^\alpha$	$\frac{\varphi\alpha\beta}{(1+\varphi\beta y)^{\alpha+1}}$	$\frac{\varphi\rho y^{\rho-1}\alpha\beta}{(1+\varphi\beta y^\rho)^{\alpha+1}}$
	$h(\theta)$	θ	$\ln[\theta/(1-\theta)]$	$\ln(\theta)$	$-\theta$	$-\theta$
	$g(\theta)$	$-\frac{1}{2}\theta^2$	$-\ln(1-\theta)$	θ	$-\ln(\theta)/\varphi$	$-\ln(\theta)/\varphi$
	ϕ	σ^2	1	1	$1/\varphi$	$1/\varphi$
	γ	$1/d$	$\alpha+\beta-2$	$1/\beta$	$\varphi(\alpha-1)$	$\varphi(\alpha-1)$
	ψ	μ	$\frac{\alpha-1}{\alpha+\beta-2}$	$\beta(\alpha-1)$	$[\beta\varphi(\alpha-1)]^{-1}$	$[\beta\varphi(\alpha-1)]^{-1}$
	$c(y,\phi)$	$-\frac{1}{2}\phi y^2-\frac{1}{2}\ln\left(\frac{2\pi}{\phi}\right)$	0	$-\ln(y!)$	$\ln(\varphi)$	$\ln\left(\varphi\rho y^{\rho-1}\right)$
	$c^*(\gamma,\psi)$	$-\frac{1}{2}\gamma\psi^2-\frac{1}{2}\ln\left(\frac{2\pi}{\gamma}\right)$	$-\ln\,B(\gamma\psi+1,\gamma-\psi\gamma+1)$	$(1+\gamma\psi)\ln\gamma-\ln\Gamma(1+\gamma\psi)$	$\frac{\gamma+\varphi}{\varphi}\ln(\gamma\psi)-\ln\Gamma\left(\frac{\gamma+\varphi}{\varphi}\right)$	$\frac{\gamma+\varphi}{\varphi}\ln(\gamma\psi)-\ln\Gamma\left(\frac{\gamma+\varphi}{\varphi}\right)$
Mean	$\mathsf{E}(Y)$	μ	$\frac{\alpha}{\alpha+\beta}$	$\alpha\beta$	$[\varphi(\alpha-1)\beta]^{-1}$	$\frac{\Gamma(\alpha-\rho^{-1})\Gamma(\rho^{-1}+1)}{(\varphi\beta)^{1/\rho}\Gamma(\alpha)}$
Variance	$\mathsf{Var}(Y)$	σ^2+d	$\frac{\alpha\beta}{(\alpha+\beta)^2}$	$\alpha\beta(\beta+1)$	$\alpha[\varphi^2(\alpha-1)^2(\alpha-2)\beta^2]^{-1}$	$\frac{1}{\rho(\varphi\beta)^{2/\rho}\Gamma(\alpha)}\left[2\Gamma(\alpha-2\rho^{-1})\Gamma(2\rho^{-1})-\frac{\Gamma(\alpha-\rho^{-1})^2\Gamma(\rho^{-1})^2}{\rho\Gamma(\alpha)}\right]$

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