Chapter 5

Mixed Models for Discrete Data

5.1 Generalized Linear Mixed Models

- The previous chapter focused on the framework of Generalized Estimating Equations
  - ▷ this can be seen as the extension of the marginal models for continuous data of Chapter 2 to the setting of categorical longitudinal responses

- In this chapter we will see the analogue of linear mixed models for categorical data

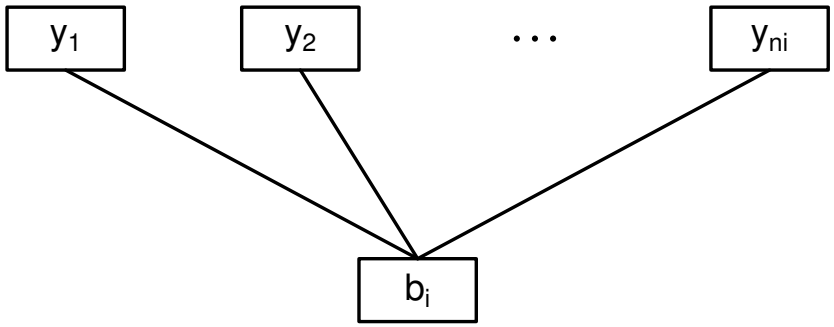
Generalized Linear Mixed Models (GLMMs)

5.1 Generalized Linear Mixed Models (cont'd)

- The intuitive idea behind GLMMs is the same as in linear mixed models, i.e.,
  - ▷ the correlation between the repeated categorical measurements is induced by unobserved random effects
  - ▷ in other words: the categorical longitudinal measurements of a subject are correlated because all of them share the *same* unobserved random effect (**conditional independence assumption**)

5.1 Generalized Linear Mixed Models (cont'd)

Graphical representation of the conditional independence assumption



5.1 Generalized Linear Mixed Models (cont'd)

- Similarly to Chapter 4, we will focus on clustered dichotomous/binary data
  - ▷ nonetheless, the same ideas and issues also apply to other categorical responses (e.g., Poisson, ordinal data, multinomial data, etc.)

- Suppose we have a binary outcome y_{ij}

$$y_{ij} = \begin{cases} 1, & \text{if subject } i \text{ has a positive response at measurement } j \\ 0, & \text{if subject } i \text{ has a negative response at measurement } j \end{cases}$$

5.1 Generalized Linear Mixed Models (cont'd)

- The generic mixed model for y_{ij} is a *Mixed-Effects Logistic Regression* and has the form:

$$\begin{cases} \log \dfrac{\pi_{ij}}{1-\pi_{ij}} = x_{ij}^\top \beta + z_{ij}^\top b_i \\ \\ b_i \sim \mathcal{N}(0, D) \end{cases}$$

where

  - $\pi_{ij} = \Pr(y_{ij} = 1)$ the probability of a positive response
  - x_{ij} a vector of fixed-effects covariates, with corresponding regression coefficients β
  - z_{ij} a vector of random-effects covariates, with corresponding regression coefficients b_i

5.1 Generalized Linear Mixed Models (cont'd)

- More formally, we have the following three-part specification

  1. Conditional on the random effects b_i, the responses y_{ij} are independent and have a Bernoulli distribution with mean $E(y_{ij} \mid b_i) = \pi_{ij}$ and variance $\text{var}(y_{ij} \mid b_i) = \pi_{ij}(1 - \pi_{ij})$

  2. The conditional mean of y_{ij} depends upon fixed and random effects via the following expression:

$$\log \frac{\pi_{ij}}{1 - \pi_{ij}} = x_{ij}^\top \beta + z_{ij}^\top b_i$$

  3. The random effects follow a multivariate normal distribution with mean zero and variance-covariance matrix D

5.1 Generalized Linear Mixed Models (cont'd)

- Notes: On the definition of GLMMs

  ▷ The three-part specification of GLMMs corresponds to a full specification of the distribution of the outcome y_{ij} – this is in contrast to the GEE approach, which is a semi-parametric method

  ▷ The mean and correlation structures are simultaneously defined using random effects
  $\Rightarrow$ As we will see next, this has direct and important implications with respect to the interpretation of the parameters

5.2 Interpretation

- Example: In the AIDS dataset, a very low CD4 count (less than 150 cells/mm^3) is an indicator for opportunistic infections

  ▷ In the following analysis we dichotomize the CD4 cell counts from the AIDS dataset using this threshold

  ▷ We fit a mixed effects logistic regression with
  * *fixed effects:* time, treatment and their interaction
  * *random effects:* random intercepts

5.2 Interpretation (cont'd)

- The model has the form:

$$\log \frac{\pi_{ij}}{1-\pi_{ij}} = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \texttt{ddI}_i + \beta_3 \{\texttt{Time}_{ij} \times \texttt{ddI}_i\} + b_i, \quad b_i \sim \mathcal{N}(0, \sigma_b^2)$$

	Value	Std.Err.	z-value	p-value
β_0	6.250	0.899	6.954	< 0.001
β_1	0.149	0.044	3.392	0.001
β_2	-0.811	0.731	-1.109	0.267
β_3	-0.029	0.059	-0.494	0.622
σ_b	6.019			

5.2 Interpretation (cont'd)

- Interpretation of fixed effects
  - ▷ At baseline for group ddC the log odds of a low CD4 cell count are on average $\beta_0 = 6.25$
    - * 95% heterogeneity interval (**not** confidence interval):
      $(\beta_0 - 1.96\sigma_b \; ; \; \beta_0 + 1.96\sigma_b) = (-5.55 \; ; \; 18.05)$
  - ▷ We translate the log odds to the probability scale: The probability of low CD4 cell count is $\exp(\beta_0)/\{1 + \exp(\beta_0)\} = 0.99807$
    - * 95% heterogeneity interval:
      $(1/[1 + \exp\{-(\beta_0 - 1.96\sigma_b)\}] \; ; \; 1/[1 + \exp\{-(\beta_0 + 1.96\sigma_b)\}]) = (0.00389 \; ; \; 1)$

5.2 Interpretation (cont'd)

- When we compare the middle point of the transformed heterogeneity interval with the transformed intercept an **important** observation is made:

  ▷ $\exp(\beta_0)/\{1+\exp(\beta_0)\} = 0.99807$

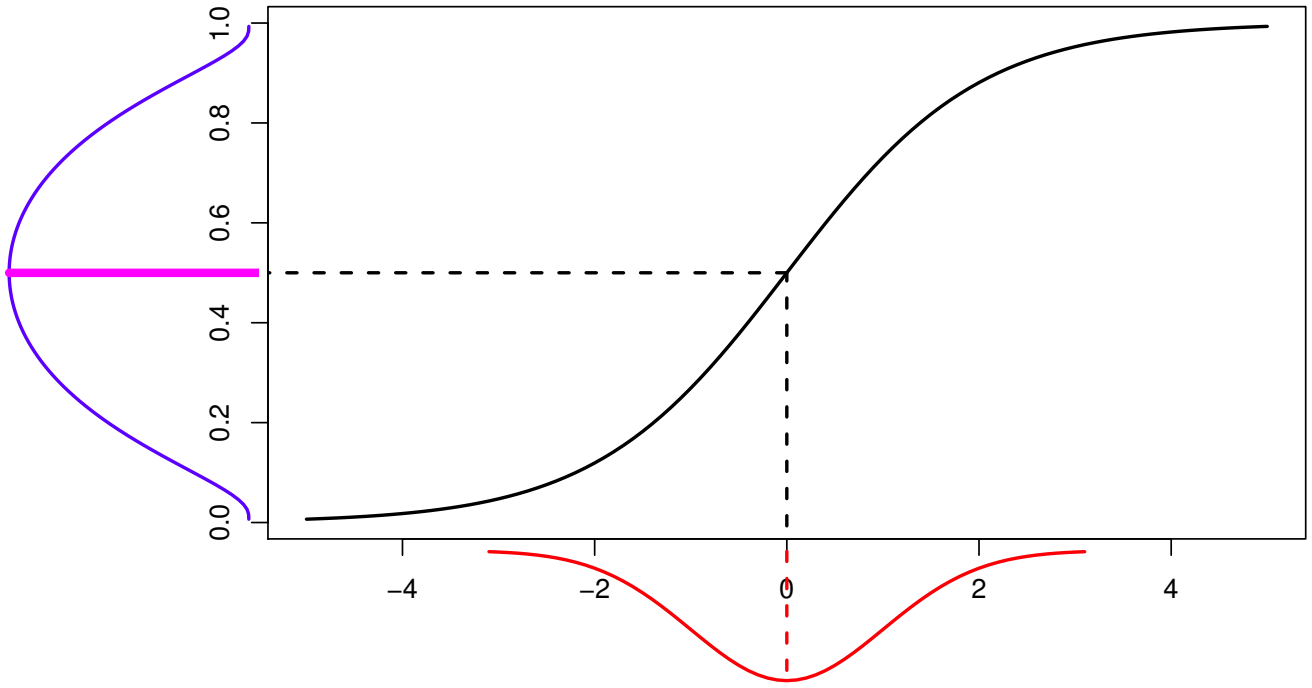
  ▷ mean of transformed interval $= 0.50194$

When we transform the fixed effects to the probability scale, they do not correspond to the average probability

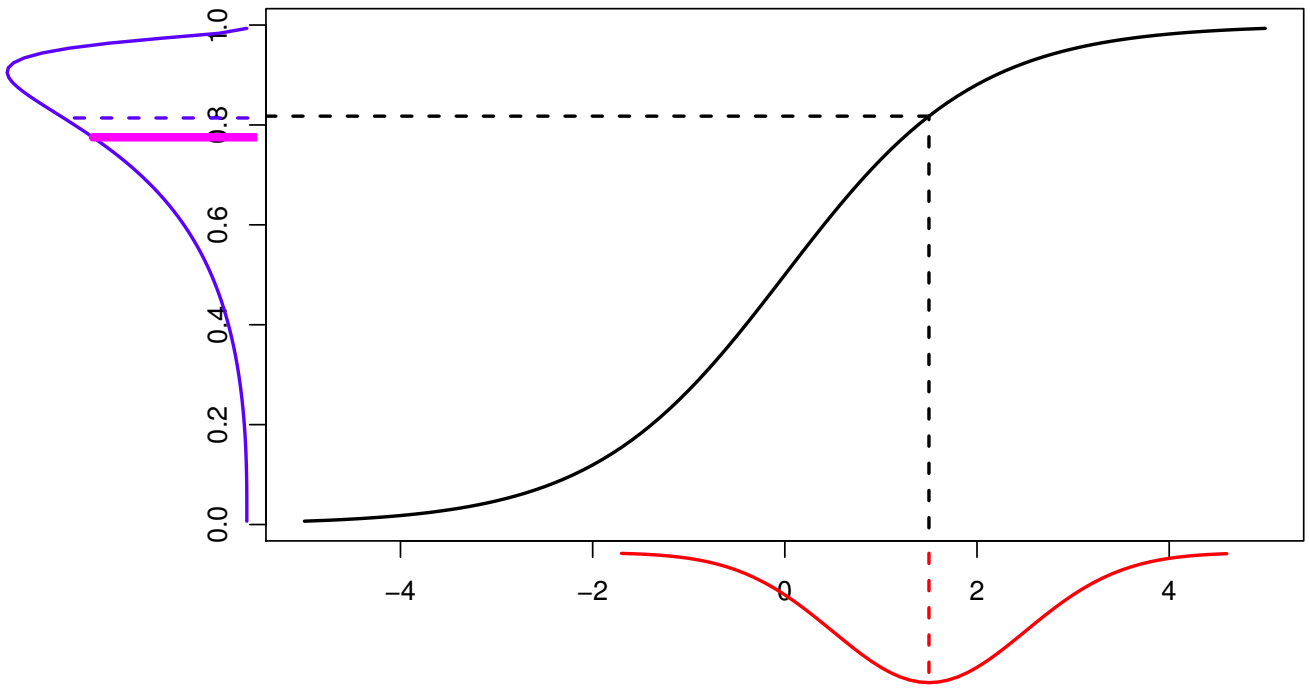
5.2 Interpretation (cont'd)

- Let's explain this issue graphically ...

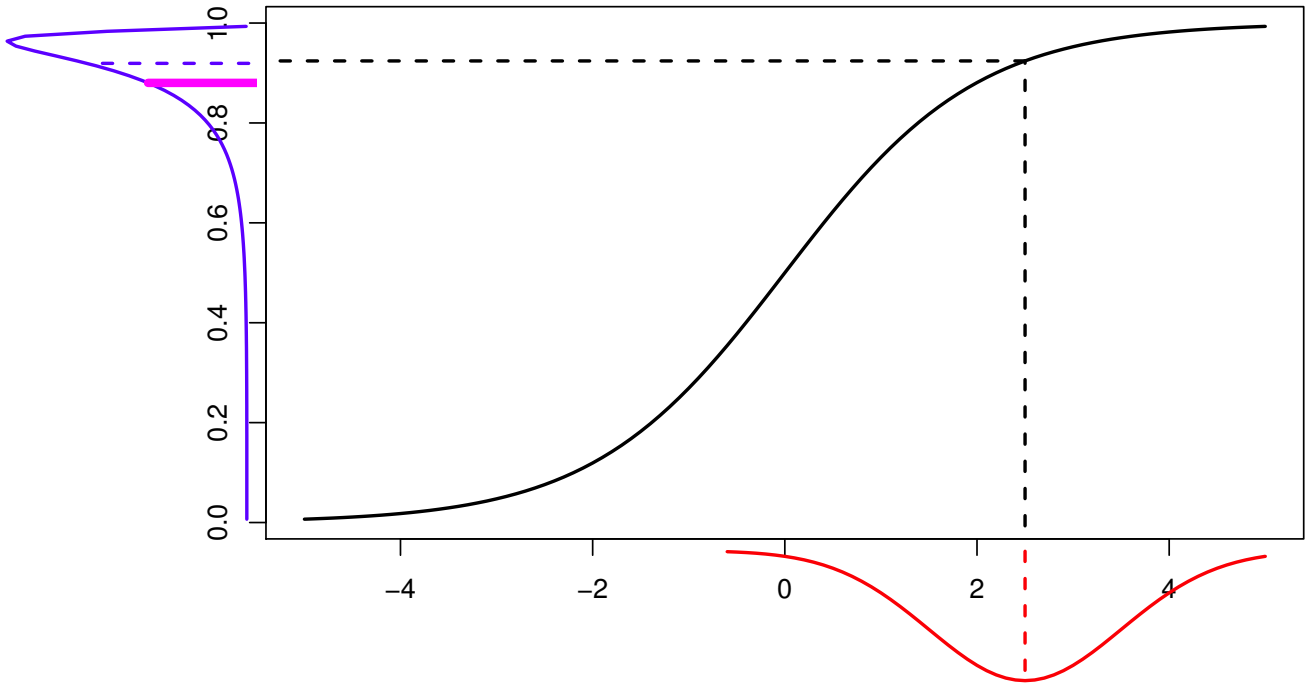
5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)

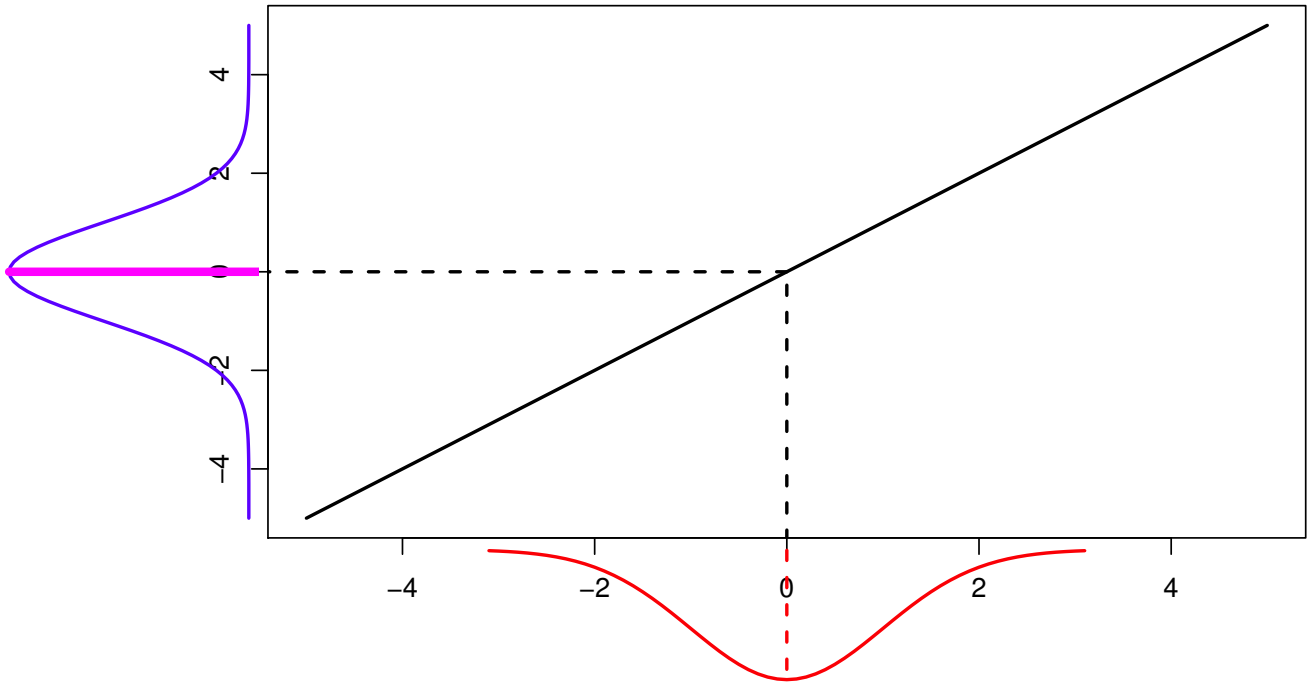


5.2 Interpretation (cont'd)

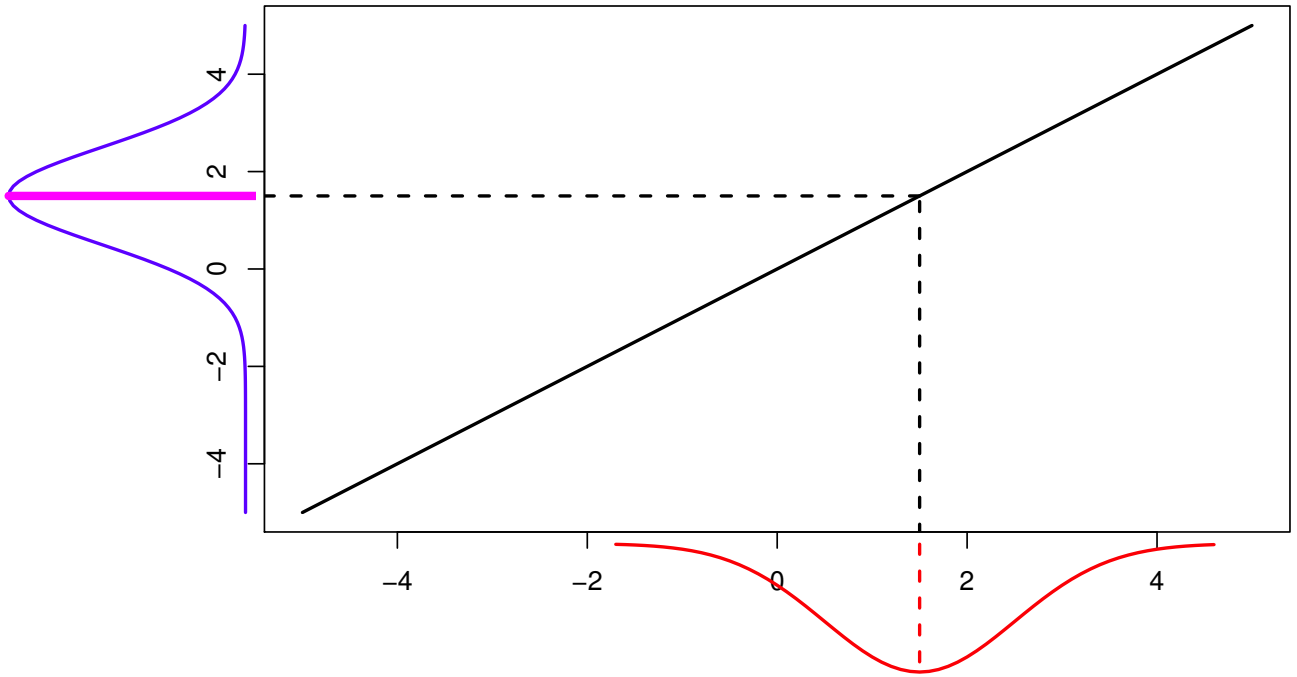
- We did not have this problem in the case of the linear mixed model because we did not have a link function
  - ▷ or to put it more precisely, the link function was the identity $g(x) = x$

- Let's see graphically again why for linear mixed models we do not have the same problem ...

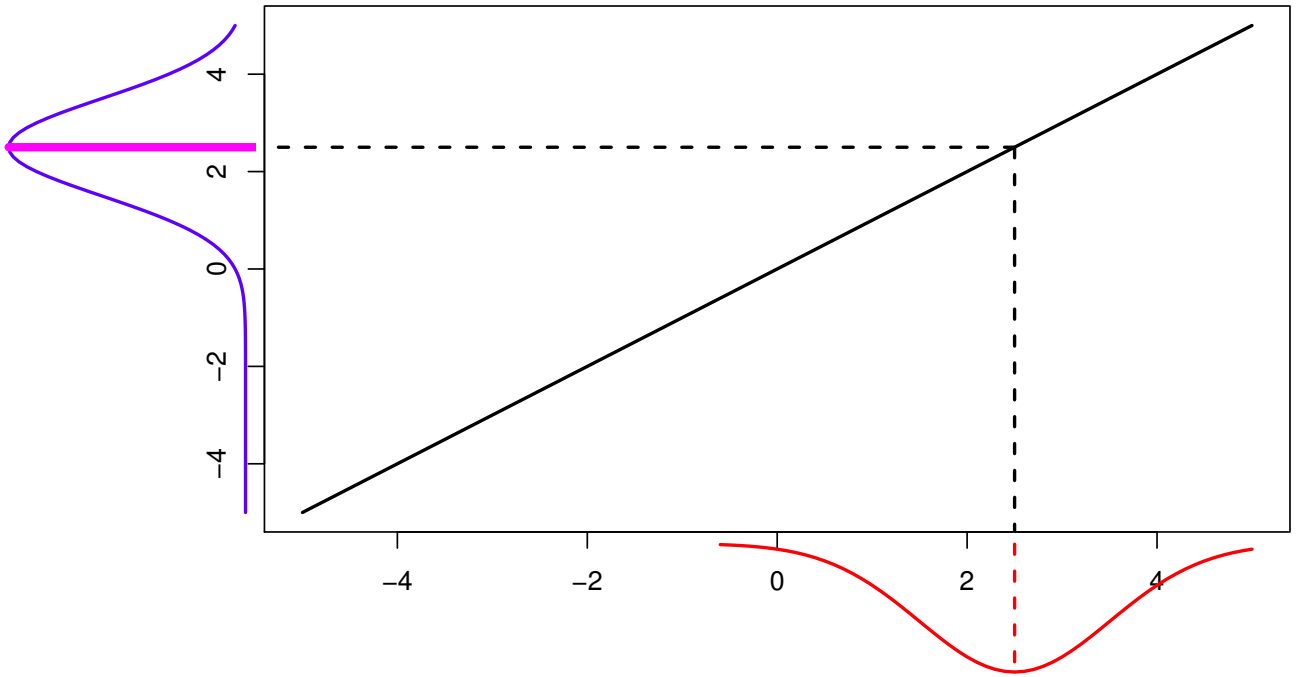
5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)

- The same complications also hold for the other fixed-effects coefficients of the logistic regression model
  - ▷ e.g., β_1 does **not** have the interpretation of the *average* odds ratio for a month increase in follow-up

- Let's see why
  - ▷ say that we compare two patients at different follow-up times who both took ddC, Patient i at month m and Patient i' at month $m+1$
  - ▷ the equation of the model for Patient i is:

$$\log \frac{\pi_{ij}}{1-\pi_{ij}} = \beta_0 + \beta_1 \{\texttt{Time}_{ij} = m\} + b_i$$

5.2 Interpretation (cont'd)

▷ the equation of the model for Patient i' is:

$$\log \frac{\pi_{i'j}}{1-\pi_{i'j}} = \beta_0 + \beta_1 \{\texttt{Time}_{ij} = m+1\} + b_{i'}$$

▷ hence, the corresponding odds ratio is:

$$\text{log odds ratio:} \quad \log \frac{\pi_{i'j}}{1-\pi_{i'j}} - \log \frac{\pi_{ij}}{1-\pi_{ij}} = \beta_1 + (b_{i'} - b_i) \Rightarrow$$

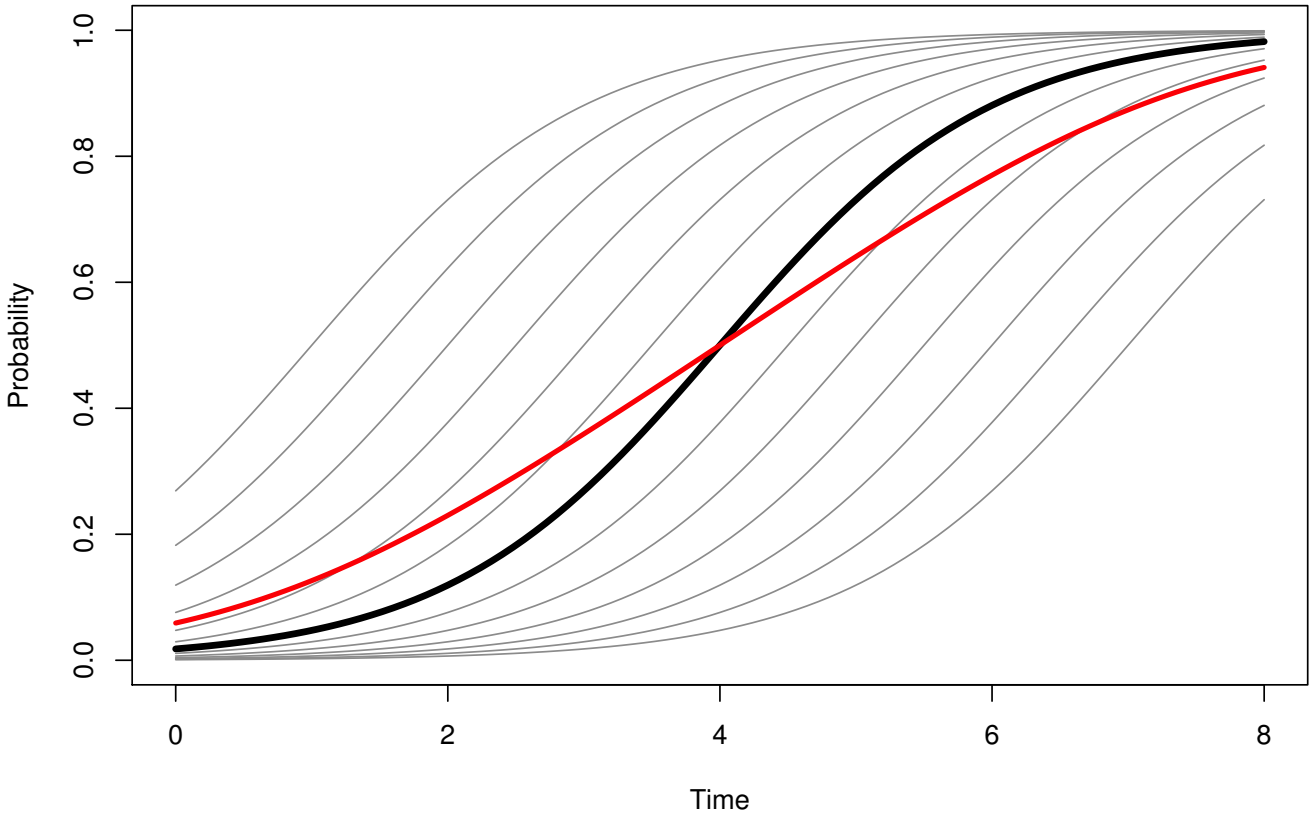
$$\text{odds ratio:} \quad \frac{\pi_{i'j}/(1-\pi_{i'j})}{\pi_{ij}/(1-\pi_{ij})} = \exp\{\beta_1 + (b_{i'} - b_i)\} \neq \exp(\beta_1)$$

5.2 Interpretation (cont'd)

- Hence, the interpretation of β_1 is not the log odds for unit increase of `Time` for all subjects, but rather for subjects with *the same random-effect value*

- To illustrate this again graphically, we depict the relationship between time and the probability of low CD4 cell counts
  - ▷ the grey lines depict 13 random subjects with increasing random effects
  - ▷ the black line corresponds to the subject with $b_i = 0$ (i.e., the mean individual) $\Rightarrow$ This line is actually $1/[1 + \exp\{-(\beta_0 + \beta_1 \texttt{Time}_{ij})\}]$
  - ▷ the red line that crosses the 13 lines denotes the average longitudinal evolution of the probability of low CD4 cells counts across subjects

5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)

- To summarize:
  - ▷ The fixed-effects regression coefficients are interpreted in terms of the effects of covariates on changes in an *individual's* transformed mean response, while holding the remaining covariates fixed
  - ▷ Because the components of the fixed effects β, have interpretations that depend upon holding b_i (the i-th subject's random effects) fixed, they are often referred to as *subject-specific* regression coefficients
  - ▷ As a result, GLMMs are most useful when the main scientific objective is to make inferences about individuals rather than population averages
  - ▷ Population averages are the targets of inference in marginal models (i.e., GEE)

5.2 Interpretation (cont'd)

Hence, contrary to the marginal and mixed effects model for continuous data (Chapters 2 & 3), the regression coefficients from marginal models for discrete data **do not** have the same interpretation as the corresponding coefficients from mixed effects models

5.2 Interpretation (cont'd)

- **Nonetheless,** for the special case of random intercepts, there is a closed-form expression to obtain the marginal regression coefficients from the subject-specific ones, i.e.,

$$\beta^M = \frac{\beta^{SS}}{\sqrt{1 + 0.346\sigma_b^2}}$$

where

  - ▷ β^M denotes the marginal coefficients
  - ▷ β^{SS} denotes the subject-specific coefficients
  - ▷ σ_b^2 denotes the variance of the random intercepts

5.2 Interpretation (cont'd)

- Example: We continue on the previous example from the AIDS dataset (see pp.316) and we compute the corresponding marginal regression coefficients

	Subject-specific				Marginal	
	Value	Std.Err.	z-value	p-value	Value	Std.Err.
β_0	6.250	0.899	6.954	0.000	1.699	0.244
β_1	0.149	0.044	3.392	0.001	0.040	0.012
β_2	−0.811	0.731	−1.109	0.267	−0.220	0.199
β_3	−0.029	0.059	−0.494	0.622	−0.008	0.016
σ_b	6.019					

5.2 Interpretation (cont'd)

- We observe considerable differences between the two sets of parameters

  ▷ the subject-specific odds ratio for a unit increase in time for a specific ddC patients is 0.54 (95% CI: 0.52; 0.56),

  ▷ whereas the corresponding marginal odds ratio averaged over all ddC patients equals 0.51 (95% CI: 0.5; 0.52)

  ▷ note that the lower limit of the 95% CI for the subject-specific odds ratio equals the upper limit of the 95% CI for the marginal odds ratio
  $\Rightarrow$ *the confidence intervals do not overlap*

5.2 Interpretation (cont'd)

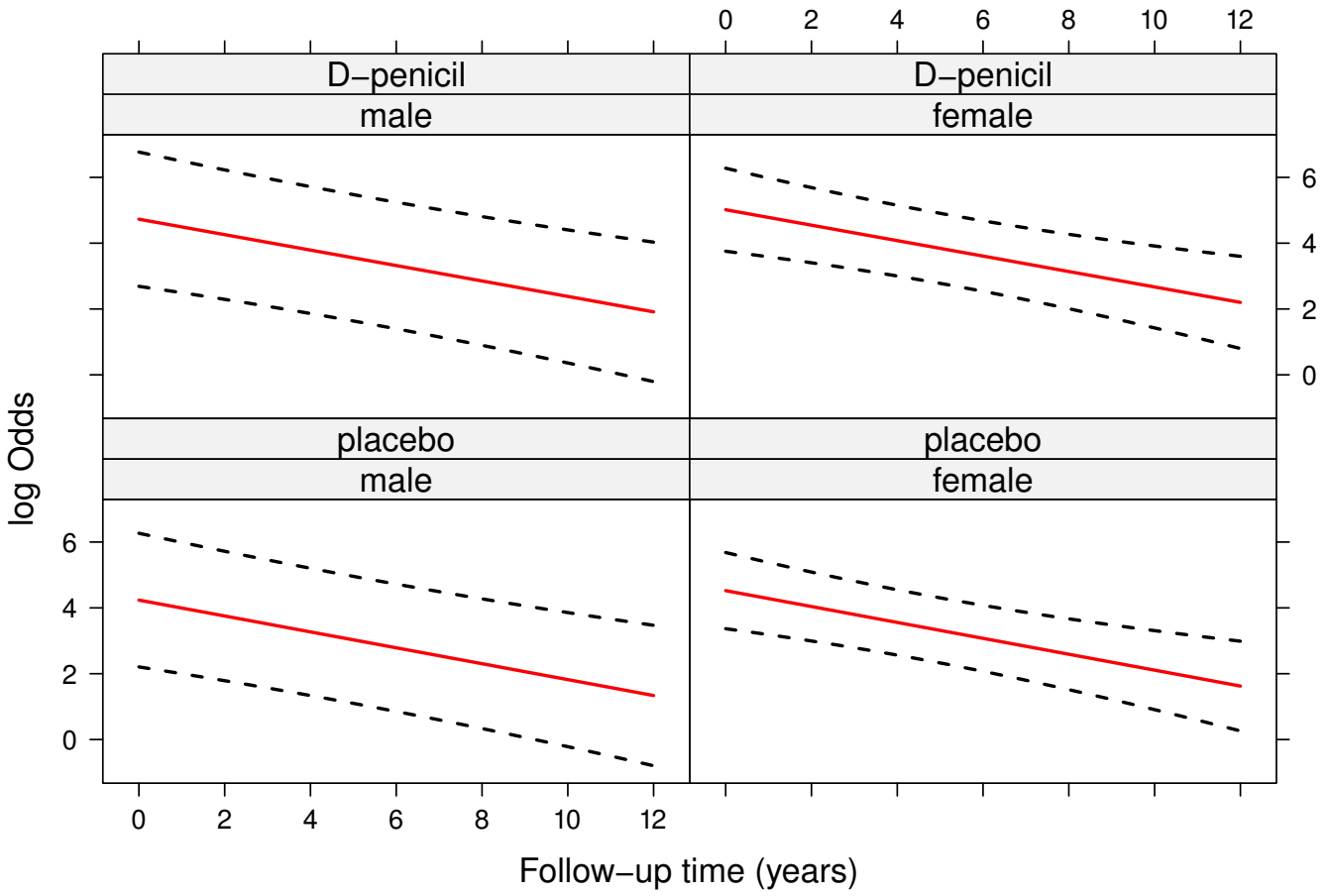
- As we have previously seen, effect plots can be used to effectively communicate complex models
  - ▷ especially in GLMMs, these plots also can be used to depict the marginal average evolutions (i.e., even if the fixed effects coefficients have a subject-specific interpretation, we can still calculate the marginal means)

- Example: In the PBC dataset we are interested in the probability of having excess serum cholesterol levels
  - ▷ we include the main effects of time, drug, age & sex
  - ▷ the interaction effect between time and drug, and the interaction effect between age and sex

5.2 Interpretation (cont'd)

- In the following figure we depict the marginal odds ratio as a function for time, separately for each combination of randomized treatment and sex

5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)

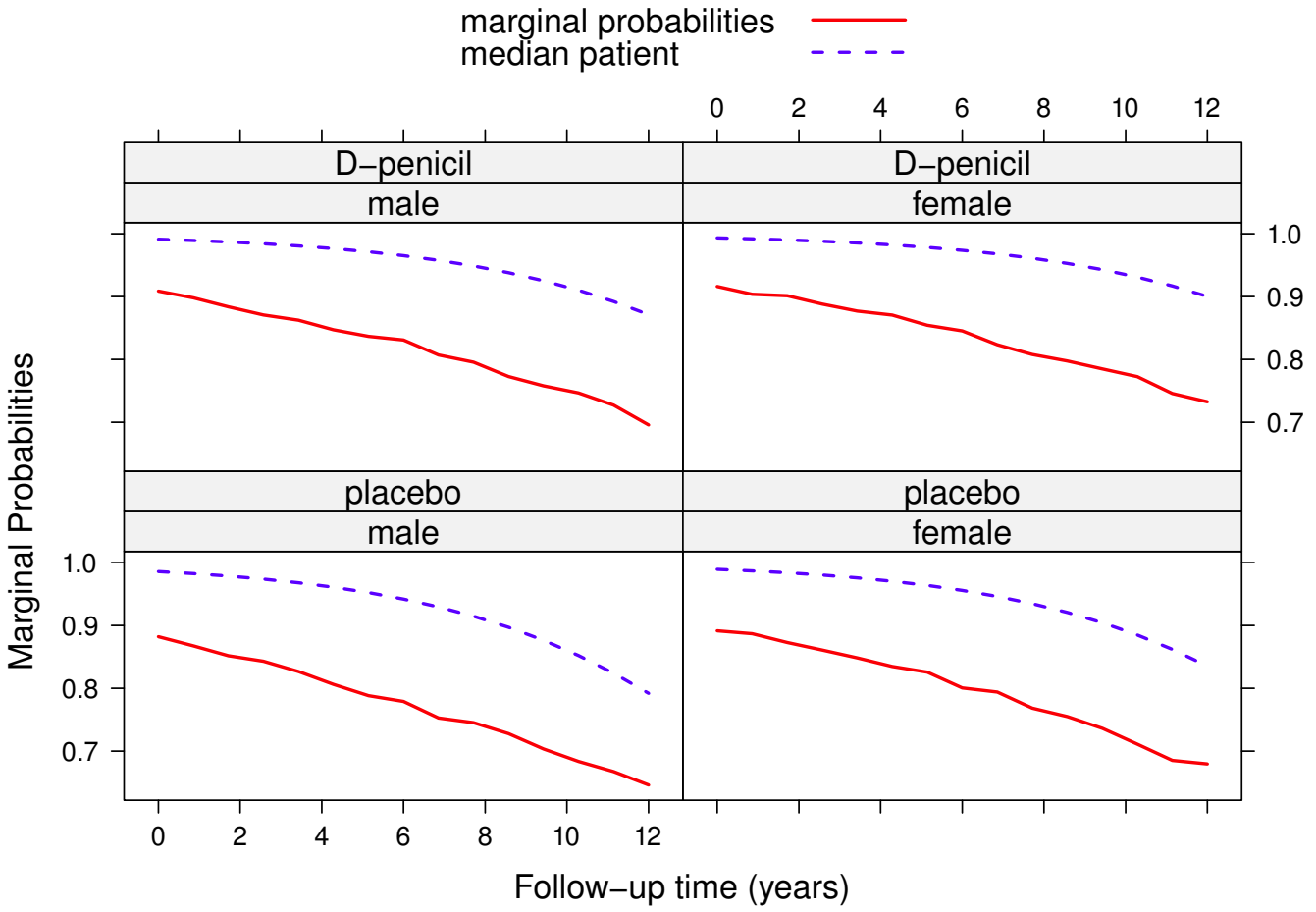
- In the following figure we depict
  - ▷ the marginal probabilities, and
  - ▷ the probabilities of the median patient

  as a function for time, separately for each combination of randomized treatment and sex

5.2 Interpretation (cont'd)

- The marginal probabilities are obtained using a Monte Carlo sampling procedure
  - ▷ for each combination of follow-up time, randomized treatment and sex we generate 3000 patients with random effect values coming from the normal distribution $\mathcal{N}(0, \hat{\sigma}_b^2)$, where $\hat{\sigma}_b^2$ denotes the estimated variance of the random effects from the model
  - ▷ for each of these 3000 patients we calculate their probability of having an abnormal serum cholesterol value
  - ▷ we take as an estimate the mean of the 3000 probabilities

5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)

- Calculation of 95% confidence intervals for the estimated marginal probabilities is not a straightforward task

5.3 Estimation

- The estimation of GLMMs is based on the same principles as in marginal and mixed models for continuous data
  - ▷ i.e., we have a full specification of the distribution of the data (contrary to GEE), and hence we can use *maximum likelihood*

- Nevertheless, there is an important complication in GLMMs

The fitting of GLMMs is a computationally challenging task!

5.3 Estimation (cont'd)

- Even though the nature of this problem is of rather computational/technical nature, we will need to discuss it in more detail ...

- What is the problem?
  - ▷ The log-likelihood expression for GLMMs has the same form as in linear mixed models (see pp.160)

$$\ell(\theta) = \sum_{i=1}^{n} \log \int p(y_i \mid b_i; \theta)\, p(b_i; \theta)\; db_i$$

where θ are the parameters of the model

5.3 Estimation (cont'd)

- In linear mixed effects models both terms in the integrand

  ▷ $p(y_i \mid b_i; \theta)$

  ▷ $p(b_i; \theta)$

  are densities of (multivariate) normal distributions, and also because y_i and b_i are linearly related

> **In linear mixed effects models the integral** in the log-likelihood expression **has a closed-form solution** (i.e., we can compute it on paper)

5.3 Estimation (cont'd)

- In GLMMs the two terms of the integrand denote densities of different distributions – e.g., in mixed effects logistic regression
  - ▷ $p(y_i \mid b_i; \theta) \Rightarrow$ Bernoulli distribution
  - ▷ $p(b_i; \theta) \Rightarrow$ multivariate normal distribution

The implication is that

In GLMMs the same integral does not have a closed-form solution

5.3 Estimation (cont'd)

- To overcome this problem two general types of solutions have been proposed in the literature
  - ▷ *Approximation of the integrand:* this entails approximating the product inside the integral (i.e., $\{p(y_i \mid b_i; \theta)p(y_i \mid b_i; \theta)\}$) by a multivariate normal distribution for which the integral has a closed-form solution
    - * Penalized Quasi Likelihood (PQL)
    - * Laplace approximation
  - ▷ *Approximation of the integral:* this entails approximating the whole integral (i.e., $\int p(y_i \mid b_i; \theta)p(y_i \mid b_i; \theta)db_i$) by a sum
    - * Gaussian Quadrature & adaptive Gaussian Quadrature
    - * Monte Carlo & MCMC (Bayesian approach)

5.3 Estimation (cont'd)

From the two alternatives, methods that rely on approximation of the integral have been shown to be superior

- Though they are (much) more computationally demanding – they have a parameter that controls the accuracy of the approximation:
  - ▷ in Gaussian quadrature rules it is the number of quadrature points (*adaptive Gaussian quadrature with 1 point is equivalent to the Laplace approximation*)
  - ▷ in Monte Carlo/MCMC approaches it is the number of samples

5.3 Estimation (cont'd)

- Example: We continue on the AIDS example, but we now treat the time variable as a factor (i.e., categorical) – the model has the form:

$$\log \frac{\pi_{ij}}{1-\pi_{ij}} = \beta_0 + \beta_1\{\texttt{Time}_{ij} = 2\} + \beta_2\{\texttt{Time}_{ij} = 6\} + \beta_3\{\texttt{Time}_{ij} = 12\} + \beta_4\{\texttt{Time}_{ij} = 18\} + b_i$$

where

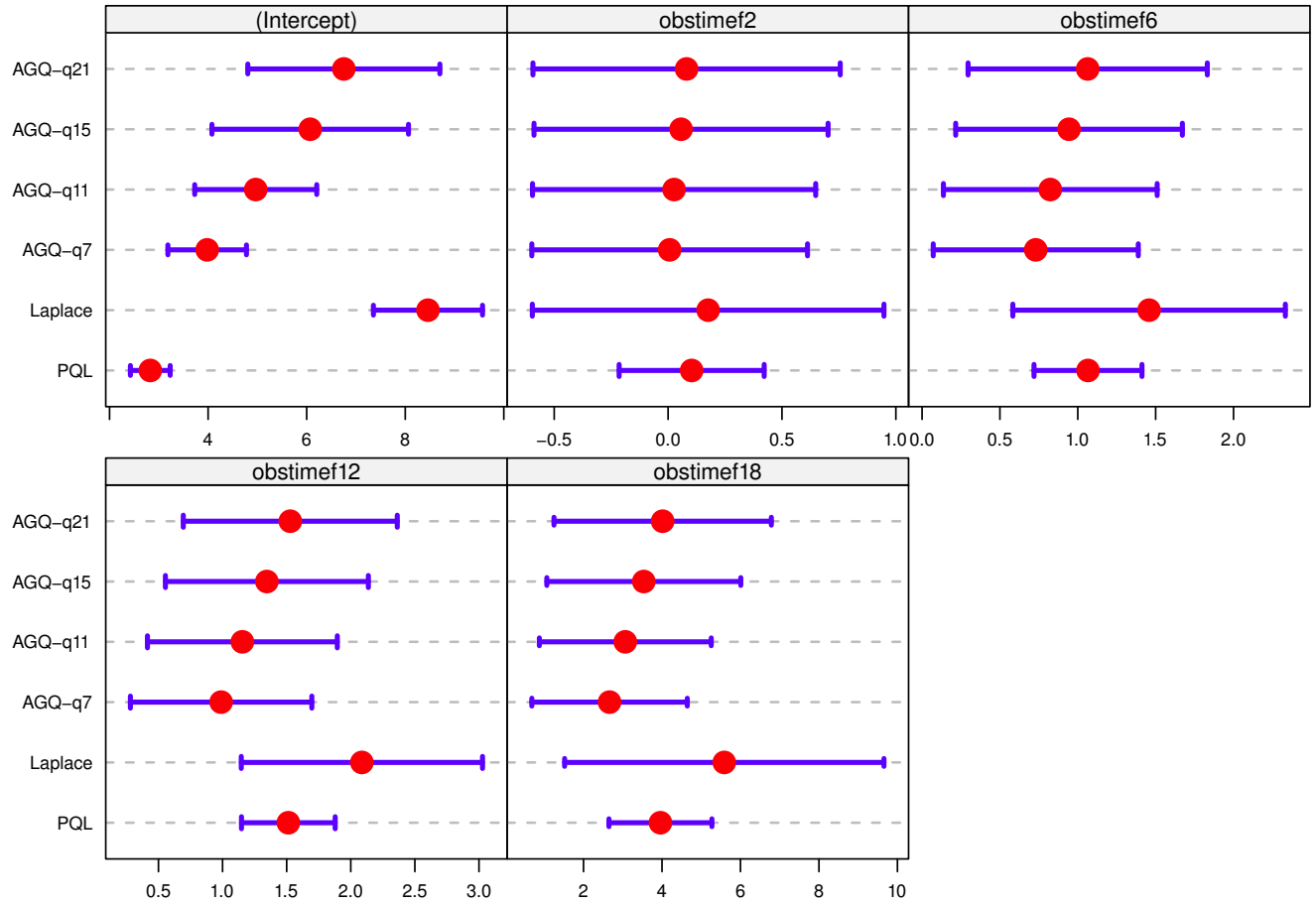
  - $\pi_{ij} = \Pr(\texttt{CD4}_{ij} < 150)$
  - $\{\texttt{Time}_{ij} = 2\}$ denotes the dummy variable for month 2, $\{\texttt{Time}_{ij} = 6\}$ the dummy variable for month 6, and so on

5.3 Estimation (cont'd)

- We have fitted this model using
  - ▷ PQL
  - ▷ Laplace approximation (adaptive Gaussian quadrature with 1 point)
  - ▷ adaptive Gaussian quadrature with 7, 11, 15 and 21 points

- The following figure depicts the estimated fixed effect coefficients under each approximation with corresponding 95% CIs

5.3 Estimation (cont'd)



5.3 Estimation (cont'd)

- We observe considerable differences between
  - ▷ PQL & Laplace (approximation of the integrand), and
  - ▷ adaptive Gaussian quadrature (approximation of the integral)

- In general, PQL and Laplace will work better as the data get more 'continuous', i.e.,
  - ▷ in Bernoulli data as the number of repeated measurements increases *considerably*
  - ▷ in Binomial data as the number of trials increases
  - ▷ in Poisson data as the rate increases

5.3 Estimation (cont'd)

- Estimation of the random effects proceeds in a similar manner as in linear mixed models (see pp.172–179)
  - ▷ based on a fitted mixed model, estimates for the random effects are based on the posterior distribution:

$$p(b_i \mid y_i; \theta) = \frac{p(y_i \mid b_i; \theta)\, p(b_i; \theta)}{p(y_i; \theta)}$$

$$\propto p(y_i \mid b_i; \theta)\, p(b_i; \theta),$$

in which θ is replaced by its MLE $\hat{\theta}$

5.3 Estimation (cont'd)

- This is a whole distribution
  - ▷ to obtain estimates for the random effects we typically use measures of location from this posterior distribution (e.g., mean or mode)
  - ▷ as an estimate of the dispersion of the random effect we use the variance of the local curvature around the mode of the posterior distribution

- Contrary to linear mixed models in which this distribution has a closed-form, in GLMMs for categorical responses this is not the case
  - ▷ calculation of the above mentioned measures of location and dispersion is achieved using numerical algorithms

5.4 GLMMs in R

R> In R there are two main packages to fit GLMMs, namely **lme4** and **MCMCglmm** – in this course we will primarily use **lme4**

- The function that fits GLMMs in **lme4** is `glmer()` – this has similar syntax as the `lmer()` function that fits linear mixed models, namely
  - ▷ `formula`: a formula specifying the response vector, the fixed- and random-effects structure
  - ▷ `data`: a data frame containing all the variables
  - ▷ `family`: a description of the error distribution and link function to be used in the model
  - ▷ `nAGQ`: the number of quadrature points

5.4 GLMMs in R (cont'd)

R> The following code fits a mixed effects logistic regression for abnormal serum cholesterol from the PBC dataset with random intercepts and 15 quadrature points for the adaptive Gauss-Hermite rule

```
glmmFit <- glmer(serCholD ~ year * drug + (1 | id),
                 family = binomial(), data = pbc2, nAGQ = 15)

summary(glmmFit)
```

5.4 GLMMs in R (cont'd)

R> With **MCMCglmm** the same model can be fitted with the code

```
prior <- list(R = list(V = 1, fix = 1),
              G = list(G1 = list(V = 1e-03, nu = -2)))

glmmFit_mcmc <- MCMCglmm(serCholD ~ year * drug , random = ~ id,
                         data = pbc2, family = "categorical",
                         prior = prior, nitt = 200000, thin = 20,
                         burnin = 5000)

summary(glmmFit_mcmc)
```

5.4 GLMMs in R (cont'd)

R> In the first part of the code we define the `prior` for the variance of the random effects – these options correspond to a non-informative prior that would be equivalent to standard maximum likelihood

R> Next in `MCMCglmm()` we have the arguments

- ▷ `fixed`: a formula specifying the response vector and the fixed-effects structure
- ▷ `random`: a formula specifying the random-effects structure
- ▷ `data`: a data frame containing all the variables
- ▷ `family`: a character vector specifying the family
- ▷ `prior`: the list of prior specifications
- ▷ `nitt`, `thin`, `burnin` the total number of iterations, the amount of thinning and the number of burn-in iterations

5.5 Model Building

- Model building for GLMMs proceeds in the same manner as for linear mixed models, i.e.,
  - ▷ we start with an elaborate specification of the fixed-effects structure that contains all the variables we wish to study, and potential nonlinear and interactions terms
  - ▷ following we build-up the random-effects structure, starting from random intercepts, next including also random slopes, quadratic slopes, etc.
    - * in each step we perform likelihood ratio tests to see whether including the additional random effect improves the fit of the model
  - ▷ having chosen the random-effects structure, we return to the fixed effects and check whether the specification can be simplified
    - * again we first start by testing the complex terms (i.e., interactions and nonlinear terms), and then we continue to drop explanatory variables, if required

5.5 Model Building (cont'd)

- **Nevertheless,** quite often, and especially for dichotomous data, extending the random-effects structure may lead to numerical/computational problems
  - ▷ this is because dichotomous data contain the least amount of information

- Hence, for dichotomous data and when we have few to moderate number of repeated measurements per subject, we often can only fit random intercepts models

5.6 Hypothesis Testing

- Having fitted a GLMM with maximum likelihood, testing of either the fixed- or random-effects structure proceeds in a similar manner as in linear mixed models

- **Important difference:** in GLMMs we do not have REML we always work with full maximum likelihood
  - ▷ when we want to test the random-effects, the fixed-effects structure is also allowed to be different (though comparing nested models is a requirement for using the standard tests)

5.6 Hypothesis Testing (cont'd)

- Example: In the PBC dataset and for the dichotomous longitudinal outcome excess serum cholesterol levels (defined as before as above the threshold of 210 mg/dL), we fit a model that postulates
  - ▷ *fixed effects:*
    - * main effects of time, treatment, and sex
    - * interaction effects between time and treatment, and between drug and sex
  - ▷ *random effects:* random intercepts

  We are interested in testing whether the model can be simplified by dropping the interaction terms

5.6 Hypothesis Testing (cont'd)

- The models under the two hypotheses are:

$$\begin{cases} H_0: \log\dfrac{\pi_{ij}}{1-\pi_{ij}} = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \texttt{D-penicil}_i + \beta_3 \texttt{Female}_i + b_i \\ H_a: \log\dfrac{\pi_{ij}}{1-\pi_{ij}} = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \texttt{D-penicil}_i + \beta_3 \texttt{Female}_i + \\ \qquad\qquad \beta_4\{\texttt{Time}_{ij} \times \texttt{D-penicil}_i\} + \beta_5\{\texttt{Female}_i \times \texttt{D-penicil}_i\} + b_i \end{cases}$$

where $\pi_{ij} = \Pr(\texttt{serChol}_{ij} > 210)$

5.6 Hypothesis Testing (cont'd)

- With respect to coefficients:

$$\begin{cases} H_0: \ \beta_4 = \beta_5 = 0 \\ H_a: \ \text{at least one different from 0} \end{cases}$$

	df	logLik	AIC	BIC	LRT	p-value
H_0	5	-353.57	717.13	742.26		
H_a	7	-353.31	720.62	755.79	0.51	0.7736

- The results suggest that the interaction terms do not seem to improve the fit of the model

5.6 Hypothesis Testing (cont'd)

- Similarly to previous chapters, when we want to test non-nested models we can use information criteria, i.e., the AIC or the BIC

5.7 Review of Key Points

- GLMMs are the analogue of linear mixed models for categorical data
  - ▷ we include random effects in the linear predictor to account for the correlations in the outcomes belonging to the same groupe/cluster

- Features of GLMMs
  - ▷ these models provide a complete specification of the distribution of the grouped/longitudinal outcome – contrary to GEE, which is a semi-parametric method
  - ▷ interpretation of parameters is conditional on the random effects – contrary to GEE, which provide coefficients with a marginal interpretation

5.7 Review of Key Points (cont'd)

- Features of GLMMs
  - ▷ estimation of GLMMs is more complex, and requires careful choice of numerical algorithms
  - ▷ **they provide valid inferences under MAR – contrary to GEE, which only provide valid inferences under MCAR**

- Model building and hypothesis testing works in the same way as in the previous models we have seen