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

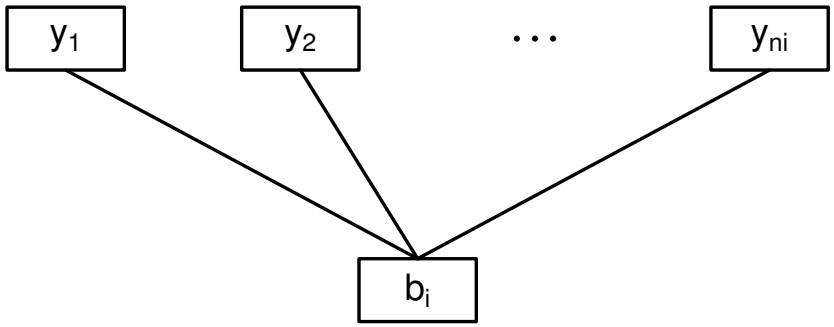
Generalized Linear Mixed Models (GLMMs)

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	5.477	0.368	14.896	< 0.001
β_1	0.141	0.041	3.410	0.001
β_2	-0.650	0.508	-1.279	0.201
β_3	-0.027	0.056	-0.484	0.628
σ_b	5.447			

5.2 Interpretation (cont'd)

- Interpretation of the fixed-effects coefficients in the mixed-effects logistic regression model
  - ▷ e.g., e^{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:

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

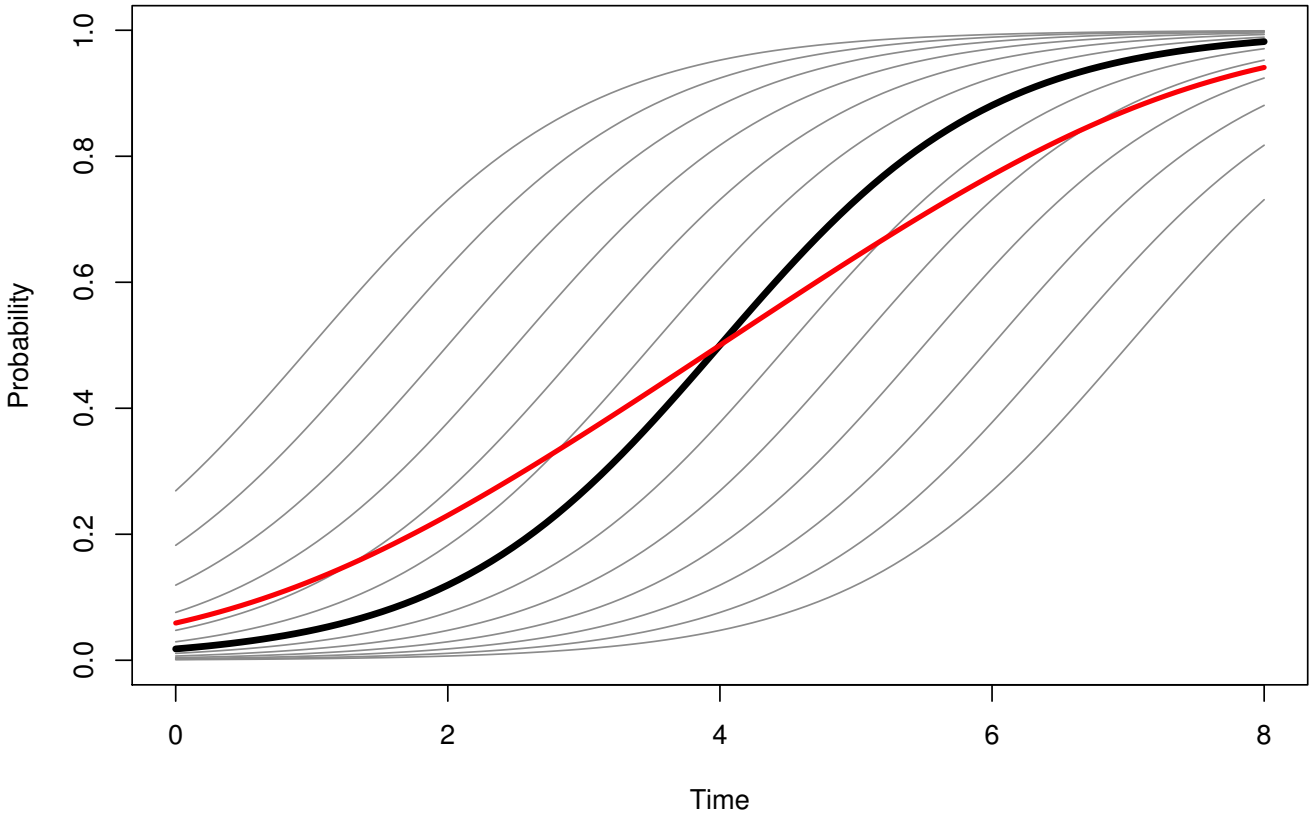
$$\text{odds ratio:} \quad \frac{\pi_{i'j}/(1-\pi_{i'j})}{\pi_{ij}/(1-\pi_{ij})} = \exp\{\beta_1 + (b_{i'} - b_i)\} \neq \exp(\beta_1)$$

5.2 Interpretation (cont'd)

- Hence, the interpretation of e^{β_1} is not the odds ratio 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...

5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)

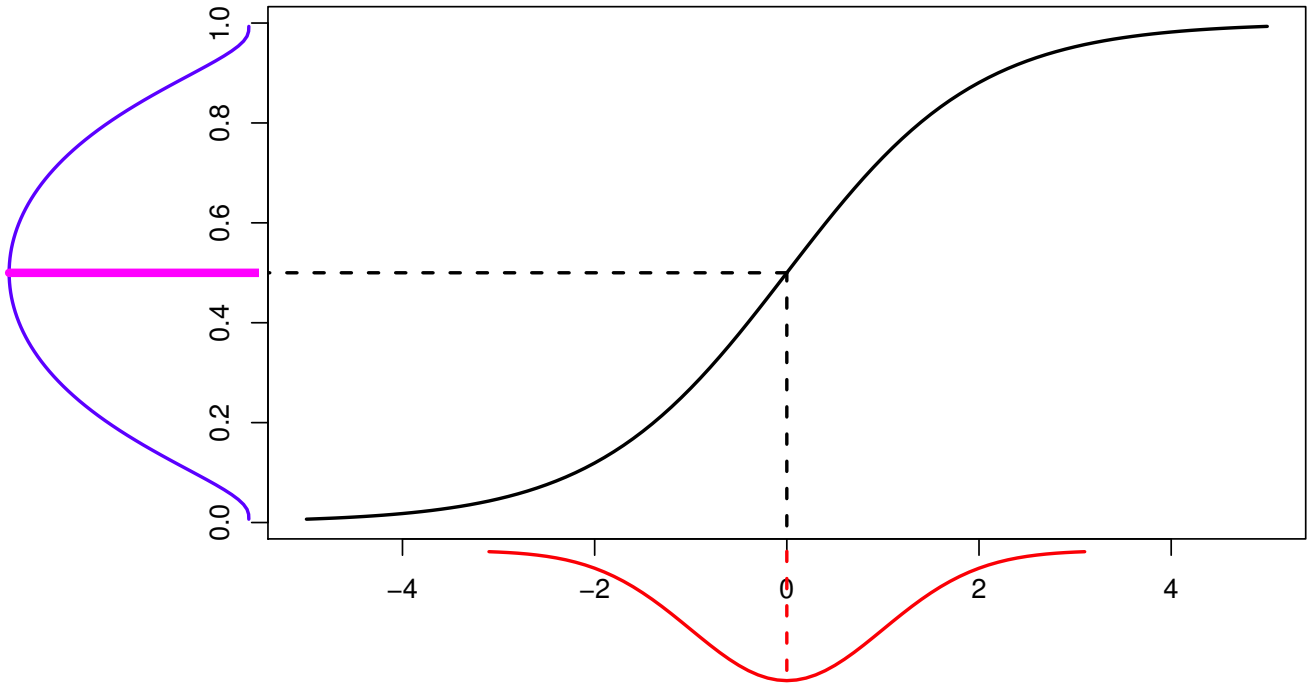
- ▷ the grey lines depict 13 random subjects with increasing random effects
- ▷ the black line corresponds to the subject with $b_i = 0$ (i.e., the mean individual)
  $\Rightarrow$ This line is actually $1/[1 + \exp\{-(\beta_0 + \beta_1 \texttt{Time}_{ij})\}]$
- ▷ the red line that crosses the 13 lines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

5.2 Interpretation (cont'd)

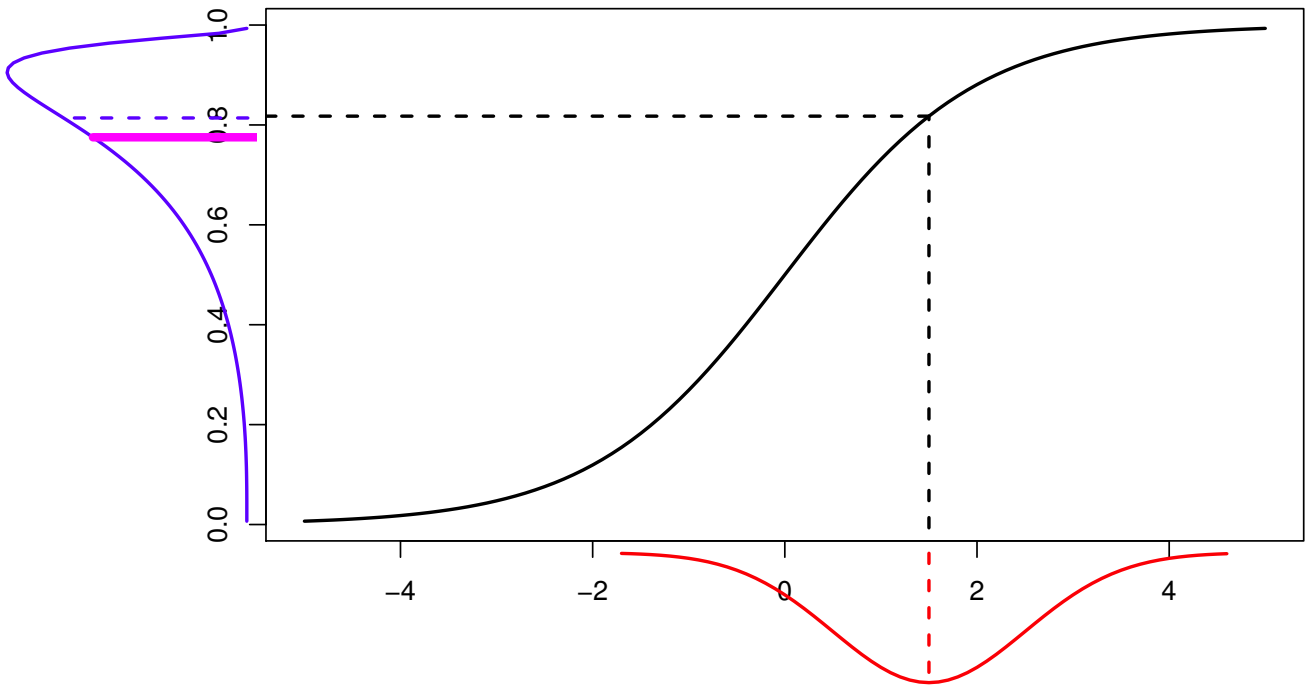
Why is this happening? ...

to connect the probabilities with covariates we need the non-linear logit function

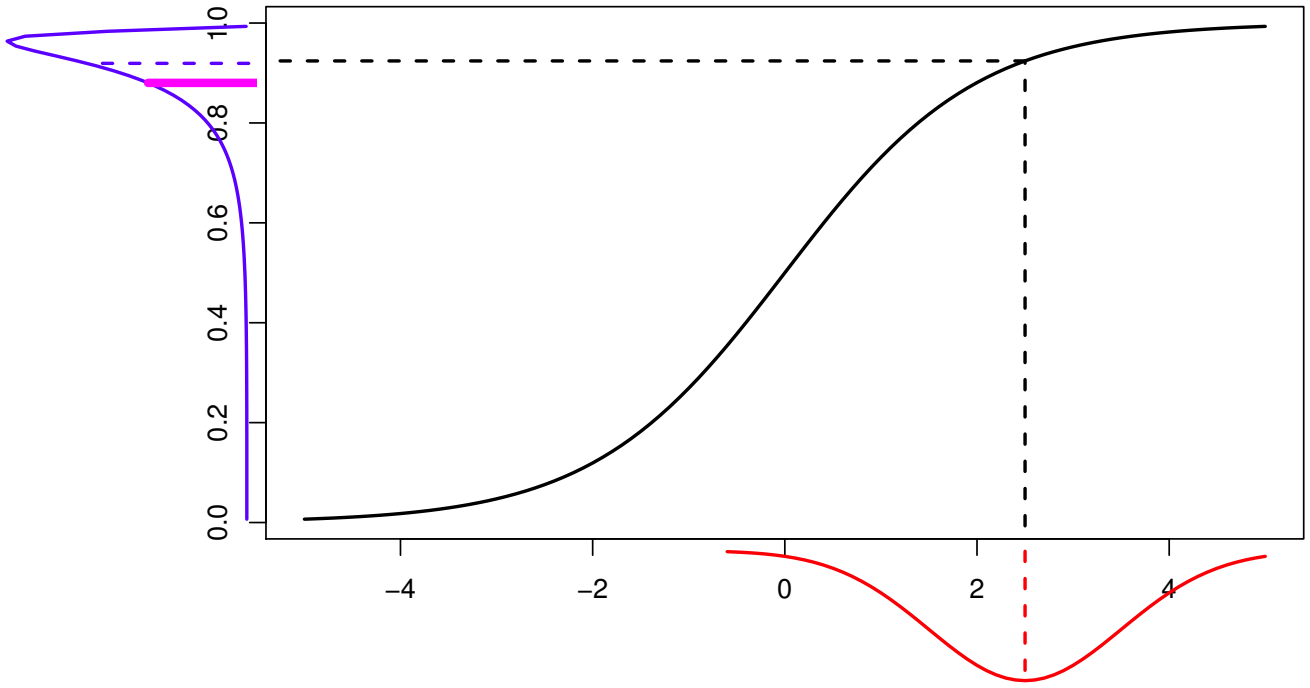
5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)

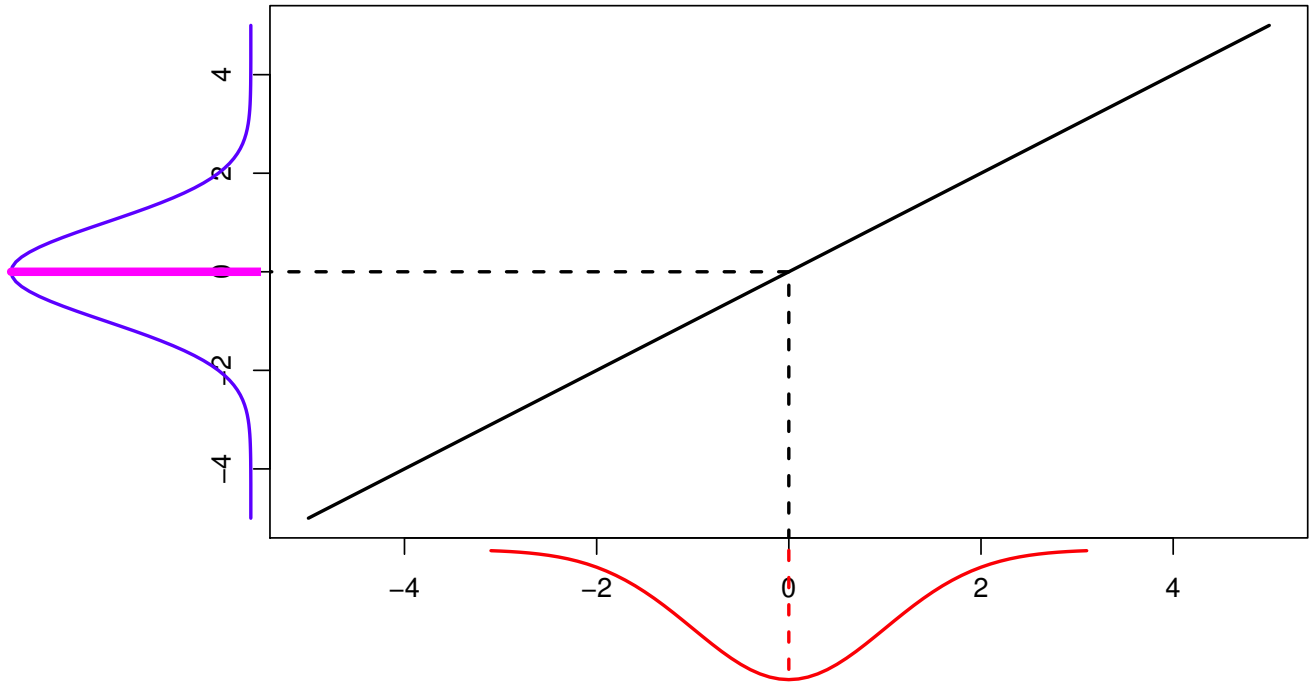


5.2 Interpretation (cont'd)

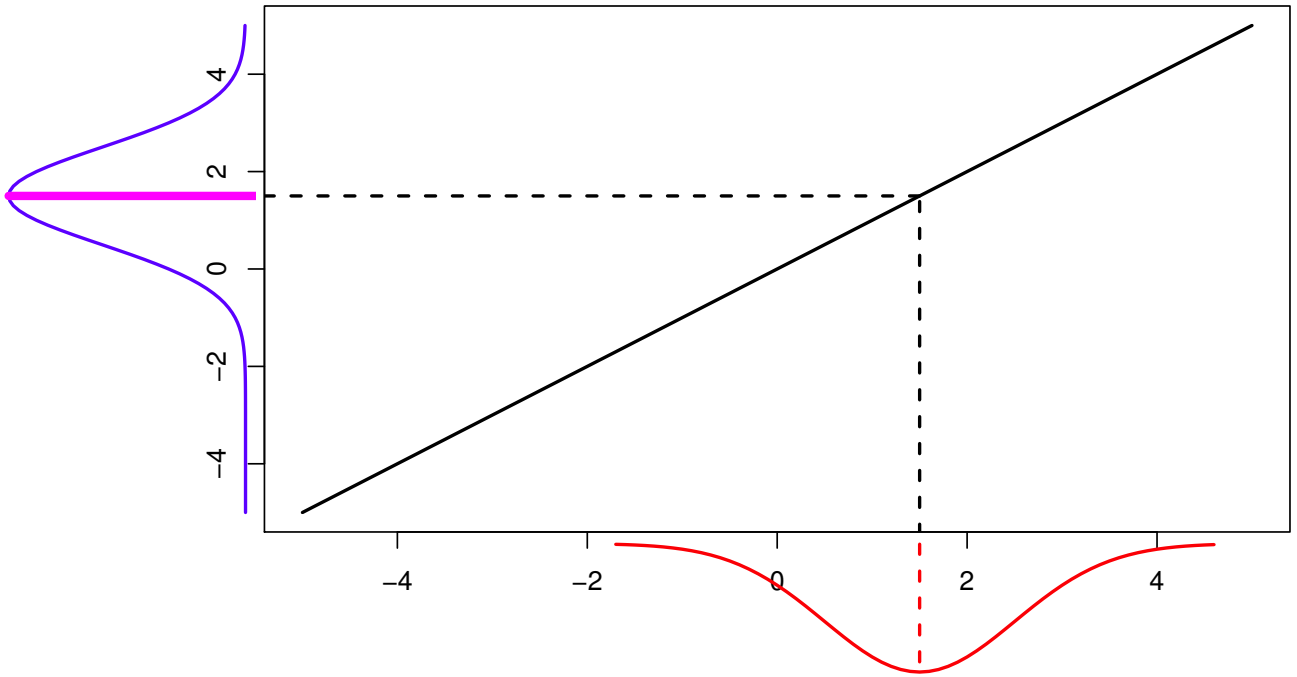
- We did not have this problem in the case of the linear mixed model because we did not have a link function
  - ▷ or to put it more precisely, the link function was the identity $g(x) = x$

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

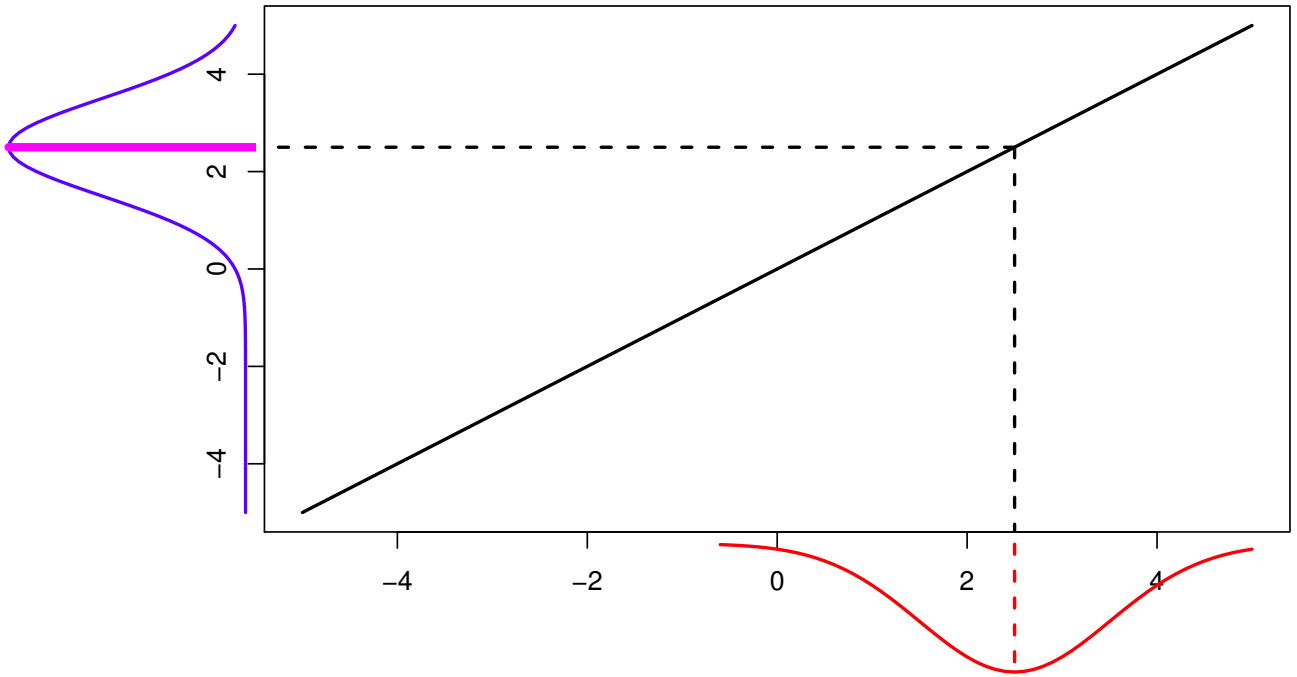
5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)

- 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)

- **However,** this formula only works for random intercepts, and cannot be used in models with more random effects

- An alternative solution has been recently proposed to overcome this issue,
  - ▷ in particular the marginal coefficients β^M are obtained as the solution to the equation

$$\beta^M = (X^\top X)^{-1} X^\top \text{logit}(\pi^M)$$

where

* X is the design matrix of the fixed effects
* $\pi_i^M = \int \text{expit}(x_i^\top \beta^{SS} + z_i^\top b_i) p(b_i)\, db_i$ are the marginal probabilities derived from the mixed model and the subject-specific coefficients

5.2 Interpretation (cont'd)

- The marginal probabilities can be obtained using a Monte Carlo sampling procedure
  - ▷ for each row of the design matrix X, we generate a random sample of subjects with random effects values coming from the normal distribution $\mathcal{N}(0, \widehat{D})$, where $\widehat{D}$ denotes the estimated covariance matrix of the random effects
  - ▷ for each of these simulated subjects we calculate the probability of $Y = 1$
  - ▷ we take as an estimate of the marginal probability the mean of the calculated probabilities of the simulated subjects

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.	z-value	p-value
β_0	5.477	0.368	14.896	< 0.001	1.588	0.135	11.802	< 0.001
β_1	0.141	0.041	3.410	0.001	0.046	0.014	3.278	0.001
β_2	-0.650	0.508	-1.279	0.201	-0.199	0.157	-1.269	0.204
β_3	-0.027	0.056	-0.484	0.628	-0.010	0.019	-0.509	0.611
σ_b	5.447							

5.2 Interpretation (cont'd)

- We observe considerable differences between the two sets of parameters

  ▷ the subject-specific odds ratio for a unit increase over time for a specific ddC patients is 1.15 (95% CI: 1.06; 1.25),

  ▷ whereas the corresponding marginal odds ratio averaged over all ddC patients equals 1.047 (95% CI: 1.019; 1.076)

  ▷ note that the lower limit of the 95% CI for the subject-specific odds ratio almost equals the upper limit of the 95% CI for the marginal odds ratio
  $\Rightarrow$ *the confidence intervals just overlap*

5.2 Interpretation (cont'd)

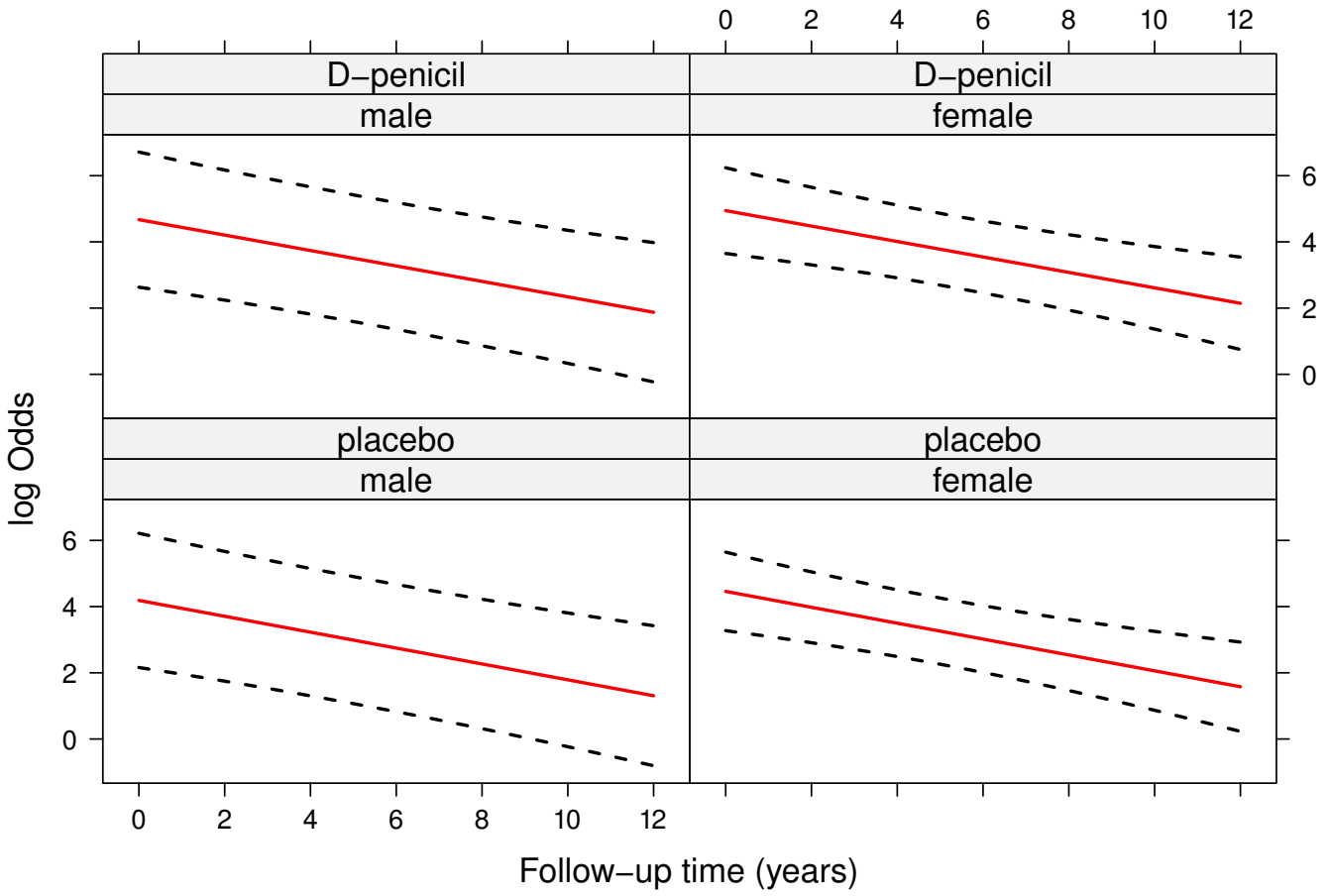
- As we have previously seen, effect plots can be used to effectively communicate complex models
  - ▷ especially in GLMMs, these plots also can be used to depict the marginal average evolutions (i.e., even if the fixed effects coefficients have a subject-specific interpretation, we can still calculate 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 log odds ratio as a function of time, separately for each combination of the randomized treatment and sex, for the average/median patient
  - ▷ average/median patient is the one with random effects values equal to zero

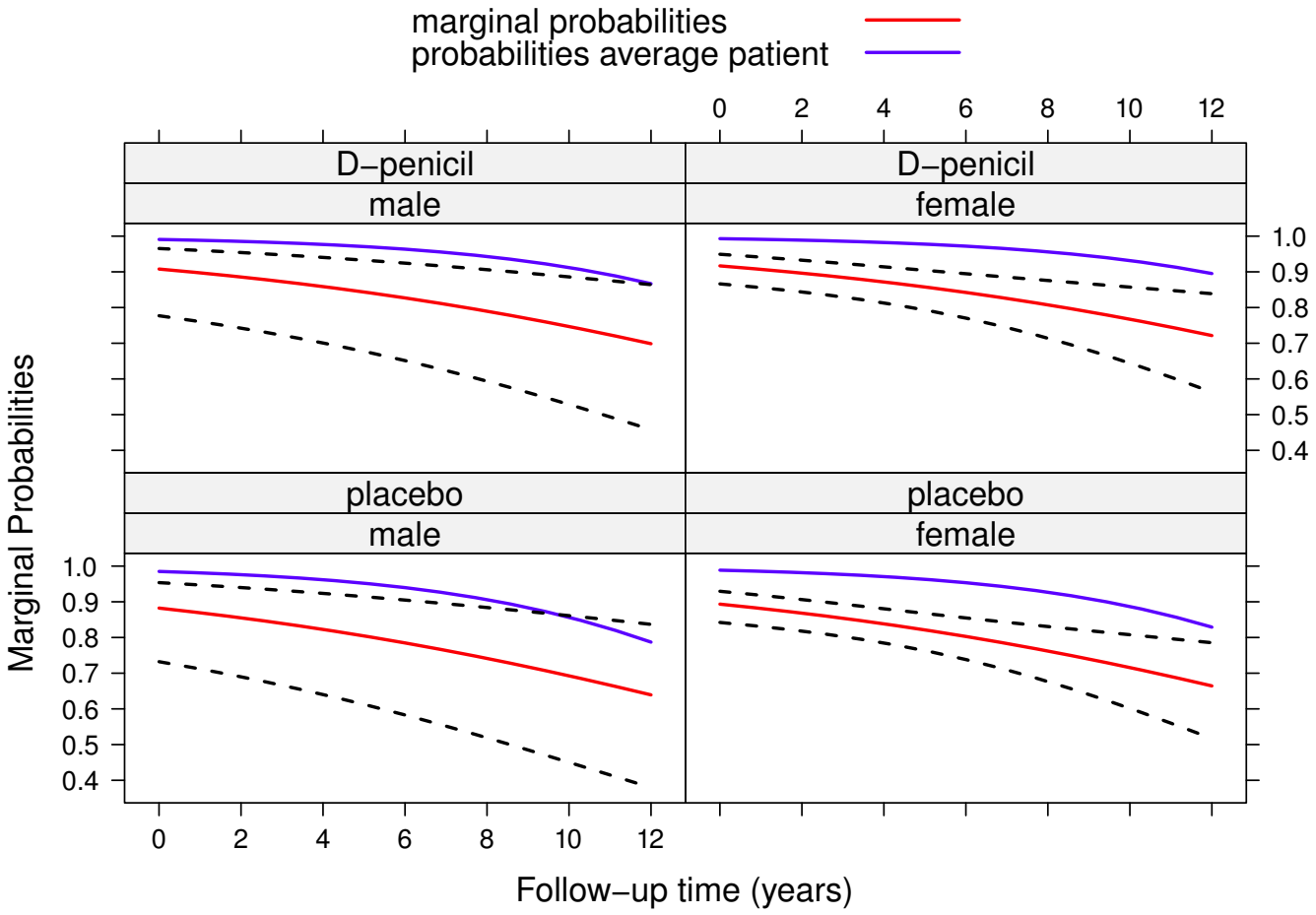
5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)

- In the following figure we depict the marginal probabilities, as a function for time, separately for each combination of randomized treatment and sex
  - ▷ contrary to the previous figure, these probabilities are averaged over the patients
  - ▷ they are obtained using the marginalized coefficients, presented in pp.334
  - ▷ to see the difference, the blue line corresponds to the probabilities of the average patient

5.2 Interpretation (cont'd)



5.2 Interpretation (cont'd)

- Calculation of 95% confidence intervals for the estimated marginal probabilities is based on an additional Monte Carlo scheme

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

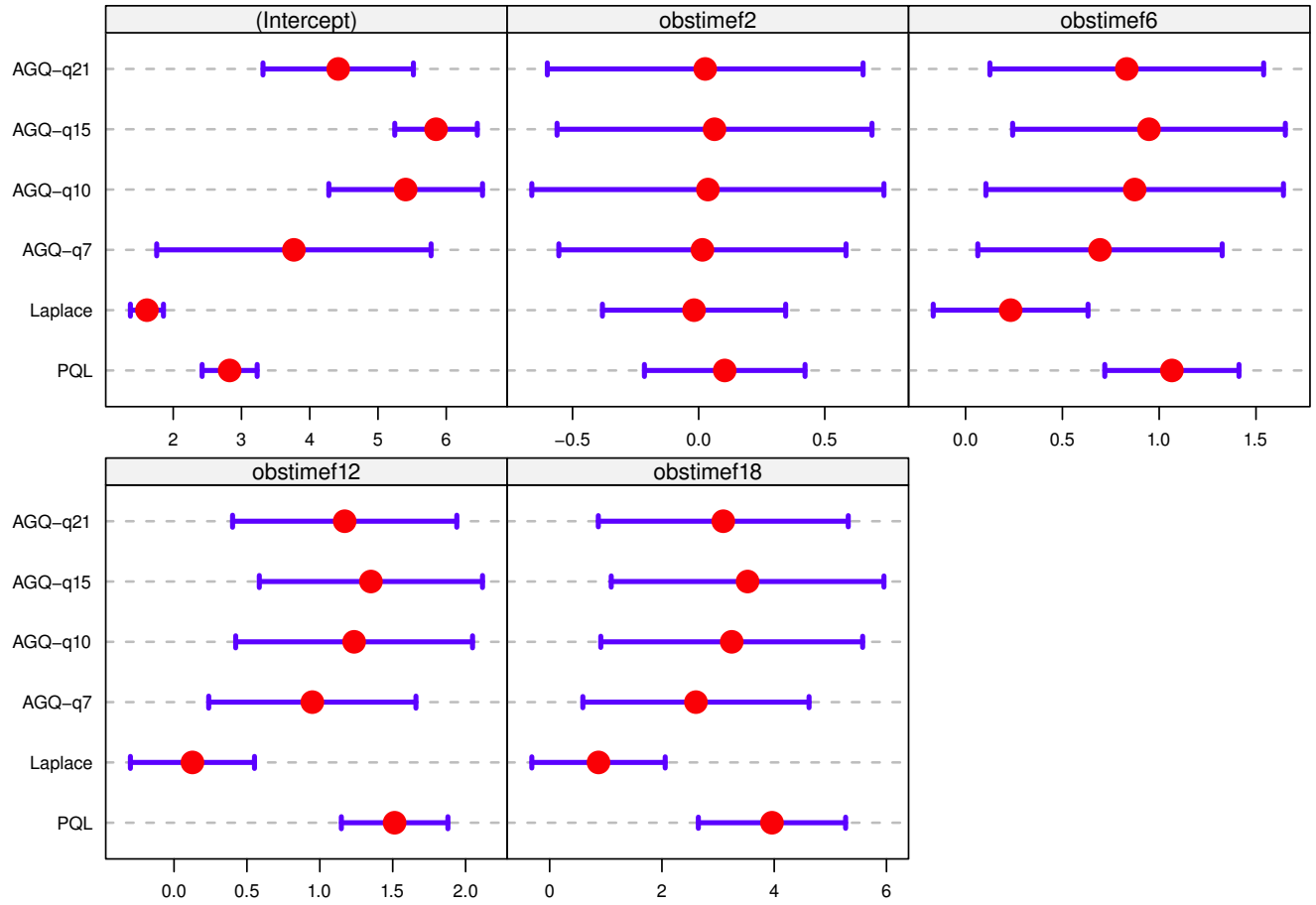
  - $\pi_{ij} = \Pr(\texttt{CD4}_{ij} < 150)$
  - $\{\texttt{Time}_{ij} = 2\}$ denotes the dummy variable for month 2, $\{\texttt{Time}_{ij} = 6\}$ the dummy variable for month 6, and so on

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, 10, 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 several packages to fit GLMMs – in this course we are going to see **lme4** and **GLMMadaptive**

- 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 `family` object specifying the distribution of the outcome and the link function
  - ▷ `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> The function that fits GLMMs in **GLMMadaptive** is `mixed_model()`; its basic arguments are

- ▷ `fixed`: a formula specifying the response vector, and the fixed-effects part of the model
- ▷ `random`: a formula specifying the random-effects part
- ▷ `data`: a data frame containing all the variables
- ▷ `family`: a `family` object specifying the distribution of the outcome and the link function
- ▷ `nAGQ`: the number of quadrature points

R> More info & examples available at:
`https://drizopoulos.github.io/GLMMadaptive/`

5.4 GLMMs in R (cont'd)

R> To fit the same model for the PBC data as we did above with `glmer()` the code is:

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

summary(glmmFit)
```

5.4 GLMMs in R (cont'd)

- Differences between `glmer()` (package **lme4**) and `mixed_model()` (package **GLMMadaptive**)
  - ▷ `glmer()` only provides the adaptive Gaussian quadrature rule for the random intercepts case, whereas `mixed_model()` uses this integration method with several random terms.
  - ▷ `mixed_model()` currently only handles a single grouping factor for the random effects, i.e., you cannot fit nested or crossed random effects, whereas such designs can be fitted with `glmer()`
  - ▷ `mixed_model()` can fit zero-inflated Poisson and negative binomial data, allowing for random effects in the zero part

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		-353.59	717.17	735.76		
H_a	2	-353.33	720.66	720.66	0.52	0.7726

- The result suggests 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 group/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