A multinomial study (model, regression, and mixed-effects)

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The problem

Consider a random variable with multinomial distribution with three categories. In this case the probability function is given by

$$\mathbb{P}[X = x] = \frac{n!}{x_1!x_2!x_3!} p_1^{x_1} p_2^{x_2} p_3^{x_3}, \quad \text{with} \quad \sum_{i=1}^{3} p_i = 1.$$

Consider a situation with just one trial, made in n independent subjects.

Three situations:

- Without covariates, modeling directly the probabilities;
- With covariates (regression);
- With repeated measures (dependency structure/random effect).

On the Agenda

1. Find the MLEs. Provide some confidence intervals.
2. Consider two covariates for each subject and propose a regression model.
3. Do the maximum likelihood estimation for the proposed model.
4. Do a simulation study to evaluate the MLEs distribution.
5. Evaluate the coverage rate for the Wald and deviance intervals.
6. Propose a mixed model for multiple observations from the same subject.
7. Do the maximum likelihood estimation for the proposed model.

At first, getting some data

$n = 100$ independent subjects, one trial, $k = 3$ categories.

```
probs <- c(.2, .6, .2) # probabilities for each category k
library(Matrix)
```

```
##
## Attaching package: 'Matrix'

## The following object is masked from 'package:tidyr':
##
##     expand
```

```
data_generator <- function(n, k = 3, p) {
    data <- t(rmultinom(n, 1, prob = p))
    colnames(data) <- paste0("p", seq(k))
    return(Matrix(data))
}
set.seed(1993)
data <- data_generator(n = 100, p = probs)
data[seq(5), ]
```

Maximum Likelihood Estimators

First, we write the log-likelihood function for a single subject j

$$L(\boldsymbol{p}) = f(x_j; \boldsymbol{p}) = \begin{cases} \frac{n!}{\prod_{i=1}^{k} x_i!} \prod_{i=1}^{k} p_i^{x_i}, & \text{when } \sum_{i=1}^{k} x_i = n \\ 0 & \text{otherwise,} \end{cases}, x_i \geq 0.$$

$$l(\boldsymbol{p}) = \log L(\boldsymbol{p}) = \log n! - \sum_{i=1}^{k} \log x_i! + \sum_{i=1}^{k} x_i \log p_i. \quad (1)$$

Second, we code it (next slide)

MLEs: mostrando o pau

```
multinom_lkl <- function(par, xs) {
    N <- nrow(xs) ; k <- ncol(xs)
    ## k-1, since the last parameter is taken as the complementary
    for (i in 1:(k - 1)) assign(paste0("p", i), par[i])
    p <- unlist(mget(c(ls(pattern = glob2rx("^p\\d")))))
    ps <- c(p, 1 - sum(p))
    lkl_p <- rep(1, N) %*% xs %*% log(ps)
    ## normalizing constant
    lkl_c1 <- sum(lfactorial(rowSums(xs)))
    lkl_c2 <- sum(lfactorial(xs))
    lkl <- lkl_c1 - lkl_c2 + lkl_p
    ## returning the negative of it
    return(-as.numeric(lkl))
}
```

i.e., `lkl <-` $\sum_{j=1}^{N} \log n_j! - \sum_{j=1}^{N}\sum_{i=1}^{k} \log x_{ij}! + \sum_{j=1}^{N}\sum_{i=1}^{k} x_{ij} \log p_{ij}.$

MLEs: matando o gato

```
initial_values <- c(1/3, 1/3)
library(bbmle)
names(initial_values) <- parnames(multinom_lkl) <- c("p1", "p2")
model_fit <- mle2(multinom_lkl,
                  start = initial_values, vecpar = TRUE,
                  data = list(xs = data))
## estimated probabilities
c(model_fit@coef, p3 = 1 - sum(model_fit@coef))
```

```
##        p1        p2        p3
## 0.2300425 0.5899757 0.1799818
```

Equal to the MLEs, x_i/n. Behold

```
colSums(data)/nrow(data)
```

```
##   p1   p2   p3
## 0.23 0.59 0.18
```

Some confidence intervals for the MLEs

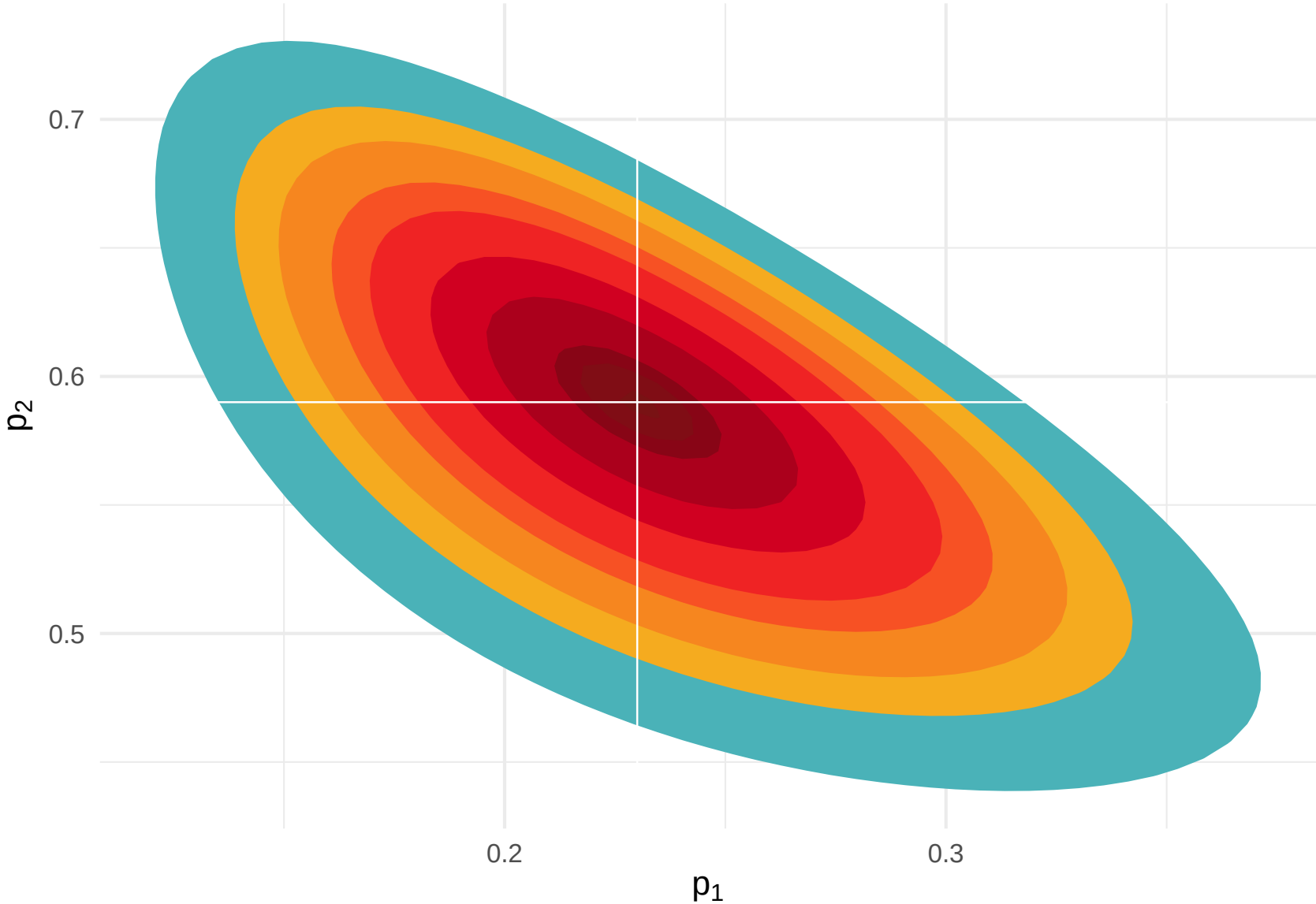
First, we write the deviance

$$\text{deviance} \equiv D(\boldsymbol{p}) = -2\,\{l(\boldsymbol{p}) - l(\hat{\boldsymbol{p}})\}.$$

It is much more simple and pretty if we work here with it, instead of the log-likelihood function itself.

```
multinom_deviance <- function(p1, p2) {
    par <- c(p1, p2)
    log_ratio <- multinom_lkl(par, xs = data) - model_fit@min
    deviance <- 2 * (log_ratio)
    return(deviance)
}
multinom_deviance <- Vectorize(multinom_deviance, c("p1", "p2"))
```

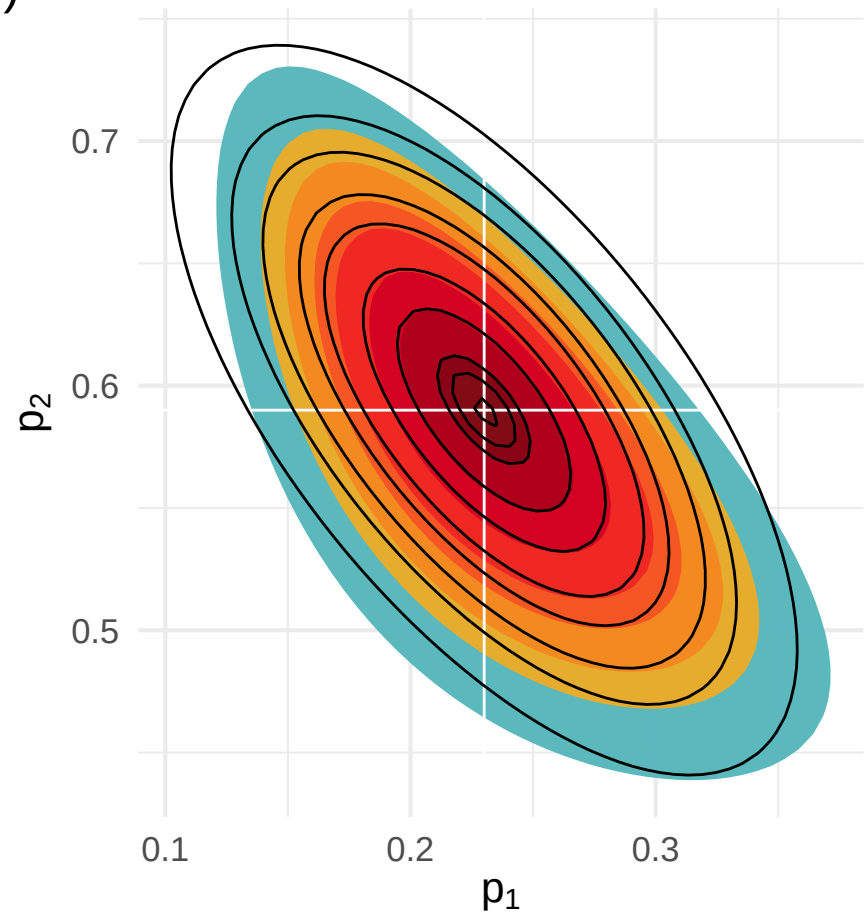
Deviance contour



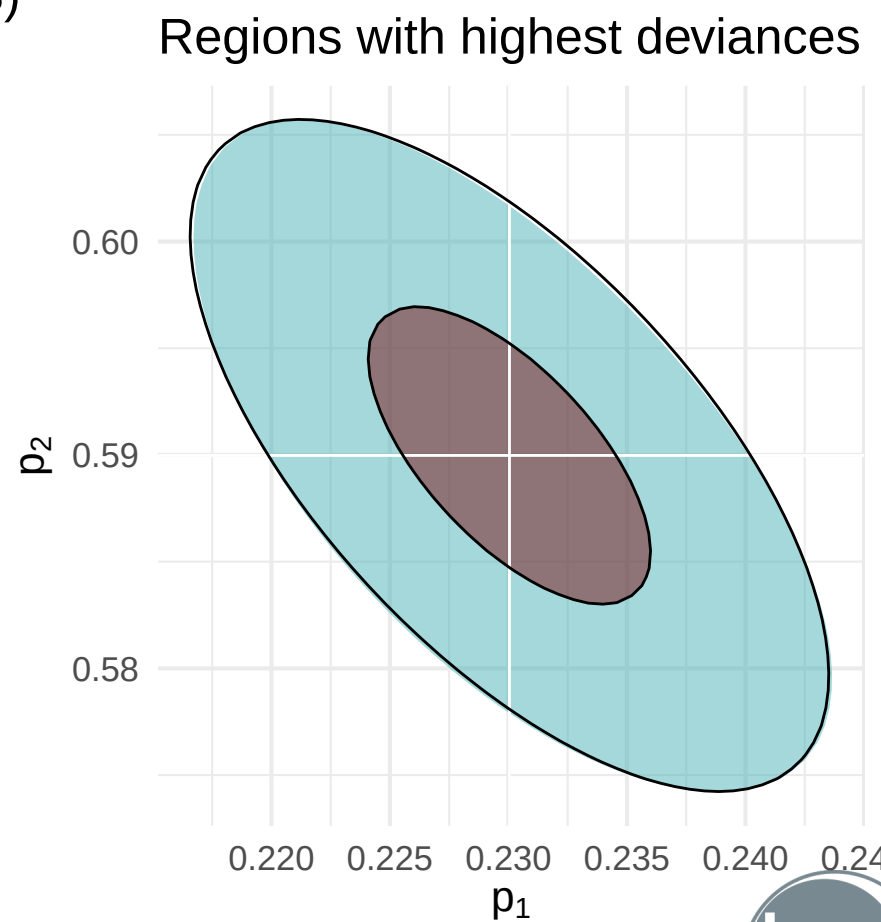
Deviance contour + quadratic approximation

Goal: confidence regions for the MLEs.

(B)



(S)



(B)ig picture and (S)mall picture.

Ok, but I also want some confidence intervals.

First, we need some stuff.

Key component: Fisher information matrix

$$I_{Expected}[\boldsymbol{p}] = \mathbb{E}\{I_{Observed}[\boldsymbol{p}]\} = \mathbb{E}\{-H_{essian}[\boldsymbol{p}]\} = \begin{bmatrix} \frac{n}{p_1} + \frac{n}{p_3} & \frac{n}{p_3} \\ \frac{n}{p_3} & \frac{n}{p_2} + \frac{n}{p_3} \end{bmatrix},$$

since $\mathbb{E}\{x_i\} = np_i$.

Thus, the asymptotic variance-covariance matrix is

$$I_{Expected}[\boldsymbol{p}]^{-1} = \begin{bmatrix} \frac{(p_2+p_3)(p_1p_2+p_1p_3+p_2p_3)}{np_2p_3} & -\frac{(p_1p_2+p_1p_3+p_2p_3)}{np_3} \\ -\frac{(p_1p_2+p_1p_3+p_2p_3)}{np_3} & \frac{(p_1+p_3)(p_1p_2+p_1p_3+p_2p_3)}{np_1p_3} \end{bmatrix}.$$

And the correlation between the estimates $\hat{p}_1$ and $\hat{p}_2$, $\hat{\rho}$, is given by

$$\hat{\rho}_{\hat{p}_1\hat{p}_2} = -\frac{\sqrt{\hat{p}_1\hat{p}_2}}{\sqrt{\hat{p}_1+\hat{p}_3}\sqrt{\hat{p}_2+\hat{p}_3}}.$$

The intervals,

A 95% Wald interval

$$\hat{p}_1 = 0.23: \quad \hat{p}_1 + \texttt{c(qnorm(0.025),qnorm(0.975))} I_{\text{Expected}}[\hat{\boldsymbol{p}}]^{-1/2}_{1,1}$$

```
## [1] 0.1475502 0.3125348
```

$$\hat{p}_2 = 0.59: \quad \hat{p}_2 + \texttt{c(qnorm(0.025),qnorm(0.975))} I_{\text{Expected}}[\hat{\boldsymbol{p}}]^{-1/2}_{2,2}$$

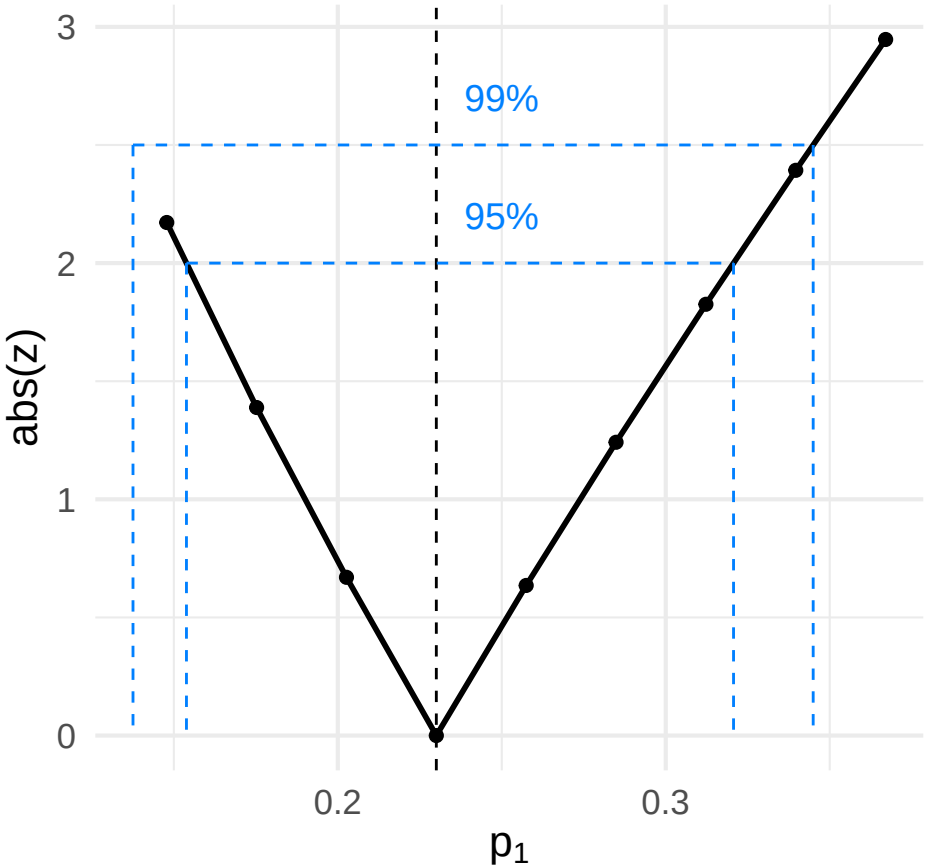
```
## [1] 0.4935764 0.6863750
```

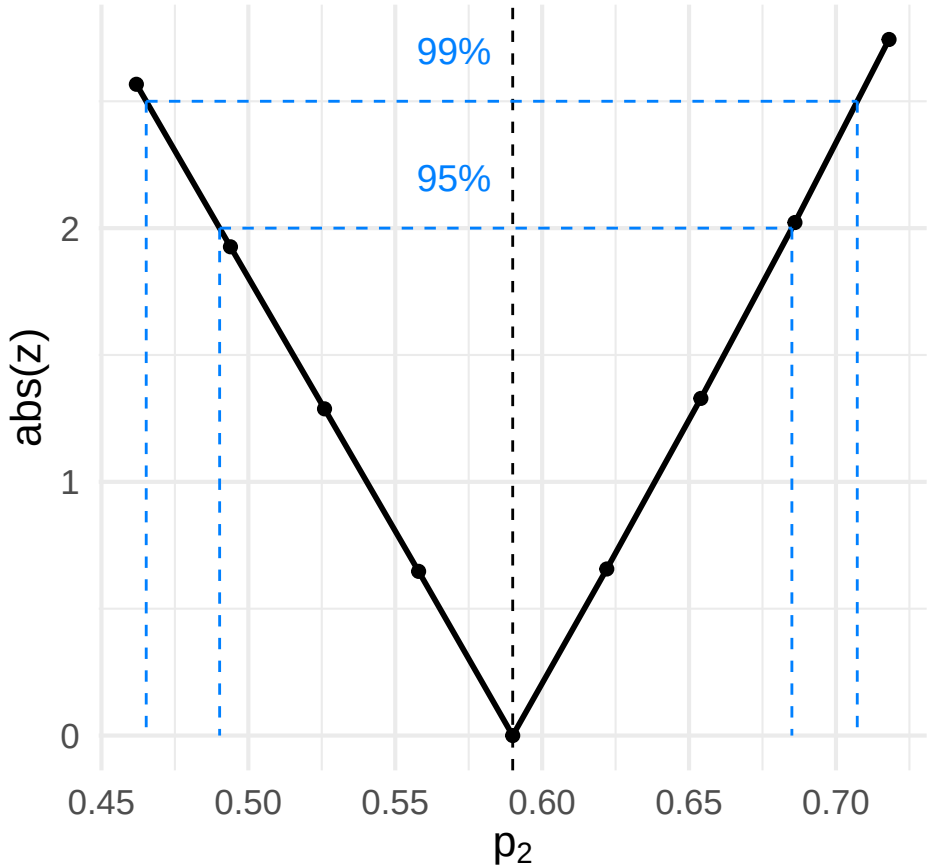
And for $\hat{p}_3 = g(\hat{\boldsymbol{p}}) = 1 - \sum_{i=1}^{2} \hat{p}_i = 0.18$, we can get a 95% CI through the multiparameter Delta Method

$$g(\hat{\boldsymbol{p}}) \pm \texttt{qnorm(0.975)} \sqrt{(\nabla g(\hat{\boldsymbol{p}}))^\top I_{\text{Expected}}[\hat{\boldsymbol{p}}]^{-1} \nabla g(\hat{\boldsymbol{p}})}$$

```
## [1] 0.1046884 0.2552752
```

And to finish this part, some likelihood profiles





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The model

$$l(\beta) = \sum_{j=1}^{N} \log n_j! - \sum_{j=1}^{N}\sum_{i=1}^{k} \log y_{ij}! + \sum_{j=1}^{N}\sum_{i=1}^{k} y_{ij} \log p_{ij},$$

$$\text{with} \quad p_{ij} = \frac{\exp\{\boldsymbol{x}_j^\top \beta_i\}}{1 + \sum_{i=1}^{k-1} \exp\{\boldsymbol{x}_j^\top \beta_i\}}.$$

- y represents the outcome for the subject j;
- i represents the multinomial category/level;
- p_{ij} is the probability of the subject j be classified in the category i, the so called inverse multinomial logit (logistic) function;
- β_i is the vector of coefficients for category i;
- and $\boldsymbol{x}_j$ is the row vector of covariates of the subject j.

Inverse multinomial logit function (the heart of everything)

```
inv_logit <- function(coefs, preds, data) {
    ## building objects
    ind_pred <- seq(preds) ; n_pred <- length(preds) ; k <- n_pred + 1
    betas <- split(coefs, substr(names(coefs), start = 3, stop = 3))
    list_X <- lapply(preds, model.matrix, data = data)
    ## computing the important stuff
    exp_xb <- sapply(seq(list_X),
                     function(i) exp(list_X[[i]] %*% betas[[i]]))
    link_denominator <- 1 + rowSums(exp_xb)
    ps <- sapply(ind_pred, function(i) exp_xb[ , i]/link_denominator)
    ps <- cbind(ps, 1 - rowSums(ps))
    colnames(ps) <- paste0("p", seq(k))
    return(list(y = data[ , seq(k)], ps = ps))
}
```

Now, simulating some probabilities

```r
n <- 100 ; k <- 3 # defining sample size and number of categories
naive_data <- function(n, k) {
    data <- as.data.frame(matrix(0, nrow = n, ncol = k))
    names(data) <- paste0("y", 1:k)
    return(data)
}
data <- naive_data(n, k)
set.seed(0080)
data$x1 <- rnorm(n, mean = 5, sd = 1) # covariates
data$x2 <- rnorm(n, mean = 1, sd = .5)
linear_pred <- list(y1 ~ x1 + x2, y2 ~ x1 + x2)
initial_values <- c("b01" = .4, "b11" = .1, "b21" = - .3,
                    "b02" = .2, "b12" = .5, "b22" = - .6)
probs <- inv_logit(initial_values, preds = linear_pred, data = data)$ps
```

After simulating the probabilities based in the covariates, we simulate the outcomes

```
summary(probs)
```

```
##        p1                  p2                  p3
##  Min.   :0.05503   Min.   :0.4361   Min.   :0.01842
##  1st Qu.:0.13533   1st Qu.:0.6810   1st Qu.:0.06418
##  Median :0.16719   Median :0.7436   Median :0.09363
##  Mean   :0.16954   Mean   :0.7323   Mean   :0.09813
##  3rd Qu.:0.20092   3rd Qu.:0.8002   3rd Qu.:0.12448
##  Max.   :0.32329   Max.   :0.9247   Max.   :0.24065
```

```
library(mc2d) # vectorized versions of {r, d}multinom
## finally, simulating the multinomial data
set.seed(1101)
data[ , seq(k)] <- rmultinomial(n, 1, prob = probs)
colSums(data[ , seq(k)]) # as expected, close to the ``probs`` means
```

```
## y1 y2 y3
## 17 76  7
```

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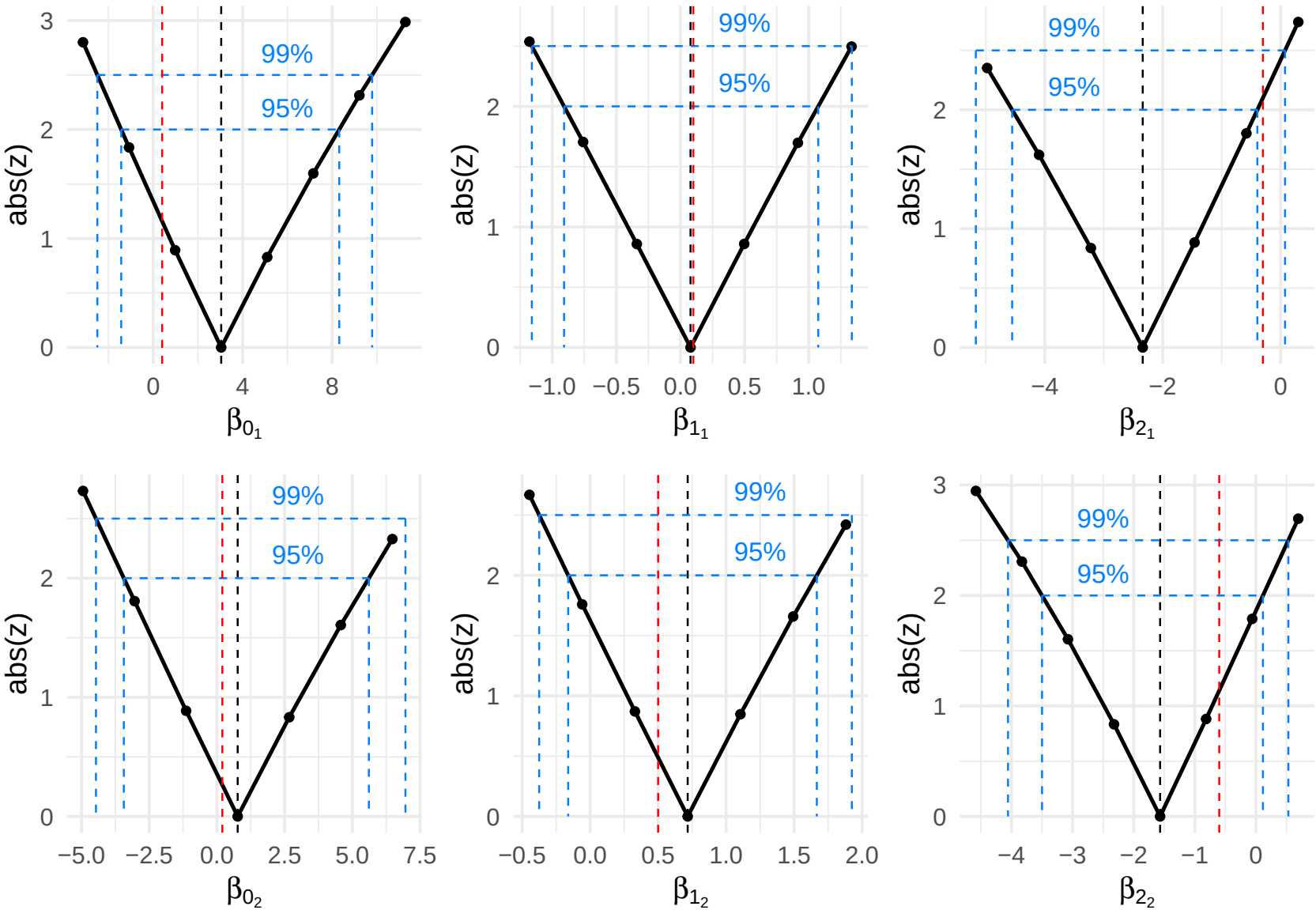
Maximum Likelihood Estimators

```
multi_lkl <- function(initial_values, linear_pred, data) {
    ilogit <- inv_logit(initial_values, preds = linear_pred, data = data)
    lkl_c1 <- with(ilogit, sum(lfactorial(rowSums(y))))
    lkl_c2 <- with(ilogit, sum(lfactorial(y)))
    lkl_p <- with(ilogit, sum(y * log(ps)))
    lkl <- lkl_c1 - lkl_c2 + lkl_p
    ## lkl <- sum(dmultinomial(as.matrix(ilogit$y), size = 1,
    ##                         prob = ilogit$ps, log = TRUE))
    return(-lkl)
}
parnames(multi_lkl) <- names(initial_values) # mle2 exigency
model_fit <- mle2(multi_lkl, start = initial_values,
                  data = list(linear_pred = linear_pred, data = data))
round(model_fit@coef, 6)
```

```
##       b01       b11       b21       b02       b12       b22
##  3.040304  0.078060 -2.338833  0.767001  0.717383 -1.568099
```

β's profile



Checking

```
model_fit@coef
```

```
##         b01         b11         b21         b02         b12         b22
##  3.04030427  0.07805955 -2.33883295  0.76700112  0.71738285 -1.56809948
```

```
fit_nnet <- nnet::multinom(y ~ x1 + x2, data_long)
```

```
coef(fit_nnet)
```

```
##    (Intercept)         x1        x2
## y1   3.0412131 0.07785772 -2.338862
## y2   0.7677984 0.71720357 -1.568073
```

```
fit_mlogit <- mlogit::mlogit(y ~ 0 | x1 + x2,
                             reflevel = 3, shape = "wide", data_long)
matrix(fit_mlogit$coef, nrow = 2, ncol = 3)
```

```
##             [,1]       [,2]      [,3]
## [1,] 3.0403108 0.07805888 -2.338837
## [2,] 0.7670852 0.71736537 -1.568101
```

Now, behold the estimated probabilities

```
results <- lapply(
    seq(k),
    function(i) cbind(inv_logit(
                    model_fit@coef, linear_pred, data)$ps[ , i],
                    probs[ , i]))
results <- do.call(cbind, results)
colnames(results) <- c(sapply(seq(k),
                              function(i) c(paste0("p", i, "_est"),
                                            paste0("p", i, "_true"))))
head(round(results, 6), 8)
```

```
##         p1_est  p1_true   p2_est  p2_true   p3_est  p3_true
## [1,] 0.044708 0.214565 0.615056 0.607281 0.340236 0.178154
## [2,] 0.069857 0.142905 0.871300 0.774907 0.058844 0.082188
## [3,] 0.123282 0.155231 0.830405 0.760373 0.046313 0.084396
## [4,] 0.182925 0.125786 0.804101 0.819901 0.012974 0.054314
## [5,] 0.108773 0.162534 0.828098 0.743764 0.063129 0.093702
## [6,] 0.149994 0.190772 0.764336 0.693429 0.085670 0.115800
## [7,] 0.229920 0.144030 0.753823 0.791296 0.016257 0.064674
## [8,] 0.088643 0.200580 0.740493 0.658897 0.170864 0.140523
```

Hypothesis tests

Some β is significantly different from zero? Testing for $\beta_{11} = 0.078$.

The simplest way is via the Wald test.

```
wald <- function(par, value, alpha) {
    mle <- as.numeric(model_fit@coef[par])
    test <- (mle - value)/sqrt(model_fit@vcov[par, par])
    critic <- qnorm(1 - alpha/2)
    print(ifelse(test <= critic, "Accept H0", "Reject H0"))
    return(c("Test" = test, "Critical_value" = critic))
}
wald(par = "b11", value = 0, alpha = .05)
```

```
## [1] "Accept H0"
```

```
##           Test Critical_value
##      0.1606135      1.9599640
```

Other options are the LRT and the Score test.

Likelihood Ratio Test (LRT)

```
lrt <- function(model_h0, model_h1, alpha) {
    test <- 2 * (model_h0@min - model_h1@min)
    critic <- qchisq(1 - alpha, df = 1)
    print(ifelse(test <= critic, "Accept H0", "Reject H0"))
    return(c("Test" = test, "Critical_value" = critic))
}
```

```
test_values <- c("b01" = .4,              "b21" = - .3,
                 "b02" = .2, "b12" = .5, "b22" = - .6)
```

```
lrt(model_h0 = mle2(multi_lkl2, start = test_values,
                    data = list(
                        linear_pred = list(y1 ~ x2, y2 ~ x1 + x2),
                        data = data, "b11" = 0)),
    model_h1 = model_fit, alpha = .05)
```

```
## [1] "Accept H0"

##           Test Critical_value
##     0.02578236     3.84145882
```

Score test

```
score <- function(par, ordered_Ie, alpha) {
    parpos <- which(colnames(ordered_Ie) == par)
    n <- ncol(ordered_Ie)
    I12 <- ordered_Ie[parpos, (parpos + 1):n]
    Vc <- ordered_Ie[parpos, parpos] -
        I12 %*% solve(ordered_Ie[-parpos, -parpos]) %*% I12
    test <- as.numeric(U[par] * 1/Vc * U[par])
    critic <- qchisq(1 - alpha, df = 1)
    print(ifelse(test <= critic, "Accept H0", "Reject H0"))
    return(c("Test" = test, "Critical_value" = critic))
}
score(par = "b11", ordered_Ie, alpha = .05)
```

```
## [1] "Accept H0"
```

```
##           Test Critical_value
##     0.02584964     3.84145882
```

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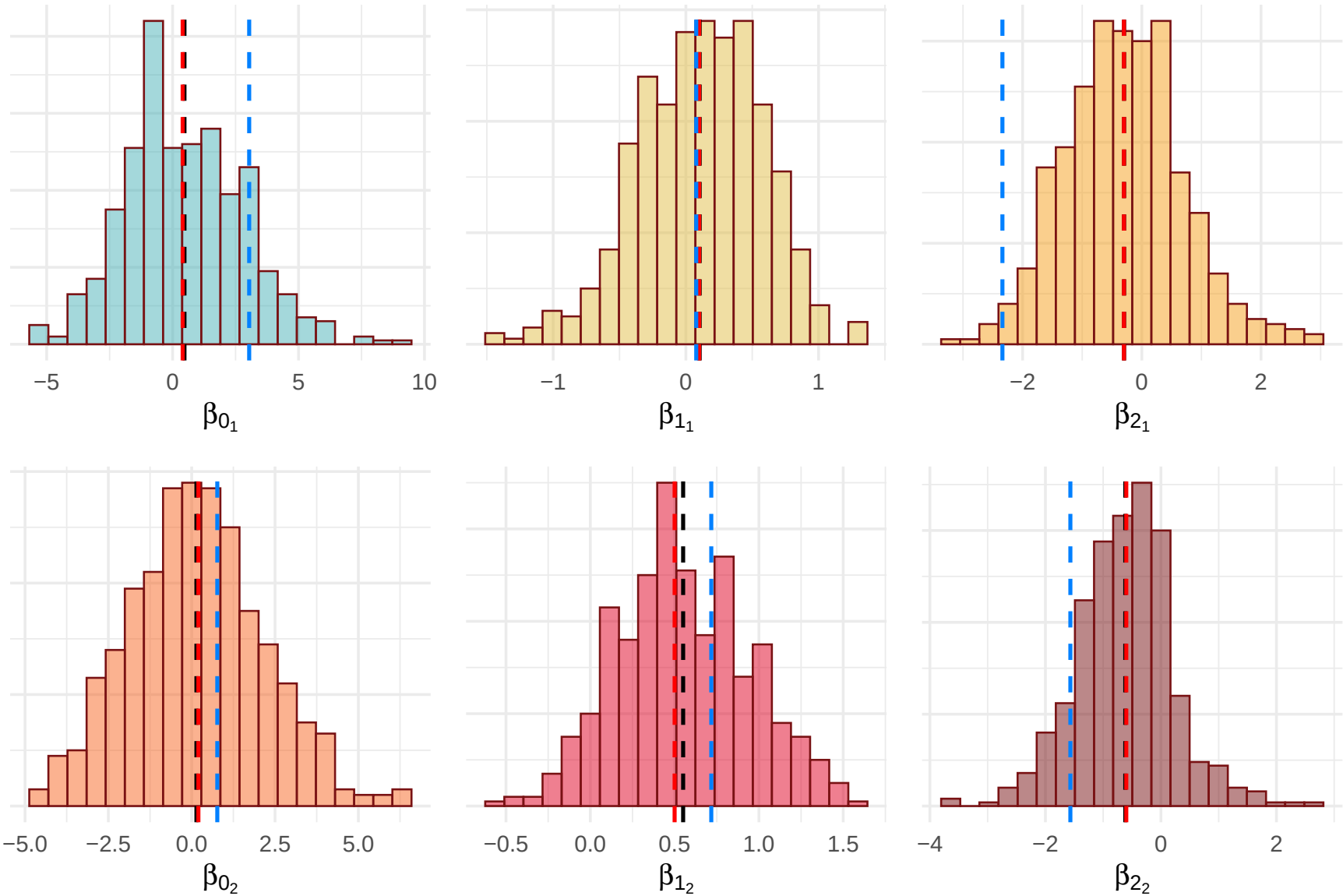
Running 500 simulations

```
library(furrr)
plan(multiprocess)
parallel2run <- function(nsimu) {
    coefs <- Matrix(0, nrow = nsimu, ncol = 6)
    confint_profile <- confint_quad <- Matrix(0, nrow = nsimu, ncol = 12)
    data[ , seq(k)] <- rmultinomial(n, 1, prob = probs)
    fit <- try(mle2(multi_lkl, start = initial_values,
                    data = list(linear_pred = linear_pred, data = data)))
    if (class(fit) != "try-error") {
        coefs[nsimu, ] <- as.numeric(fit@coef)
        confint_profile[nsimu, ] <- c(confint(fit))
        confint_quad[nsimu, ] <- c(confint(fit, method = "quad"))
    }
    return(list(coefs = coefs, confint_profile = confint_profile,
                confint_quad = confint_quad))
}
nsimu <- 500 ; simu <- vector("list", nsimu)
simu <- future_map(rep(1, nsimu), parallel2run)
```

MLEs distribution



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Coverage rate: Deviance and Wald intervals

```
coverage <- function(method) {
    coverage <- Matrix(0, nrow = 6, ncol = nsimu)
    for (i in seq(6))
        for (j in seq(nsimu))
            coverage[i, j] <-
                initial_values[i] >= simu[[j]][[method]][i] &
                initial_values[i] <= simu[[j]][[method]][i + 6]
    means <- rowMeans(coverage, na.rm = TRUE)
    names(means) <- names(initial_values)
    return(round(means, 3))}
coverage(method = 2) # deviance interval
```

```
##   b01   b11   b21   b02   b12   b22
## 0.946 0.940 0.928 0.942 0.944 0.940
```

```
coverage(method = 3) # wald interval
```

```
##   b01   b11   b21   b02   b12   b22
## 0.956 0.948 0.946 0.948 0.954 0.954
```

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For a subject i, with measurements j, we have

$$y_{ij} \mid \alpha_{1i}, \alpha_{2i} \sim \text{Multinomial}(p_{1ij}, p_{2ij}, p_{3ij}),$$

$$\text{with} \quad \begin{bmatrix} \alpha_{1i} \\ \alpha_{2i} \end{bmatrix} \sim \mathcal{N}\left[\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2_{\alpha_1} & \sigma_{\alpha_1}\sigma_{\alpha_2}\rho \\ \sigma_{\alpha_1}\sigma_{\alpha_2}\rho & \sigma^2_{\alpha_2} \end{bmatrix} \right],$$

$$\text{and} \quad p_{kij} = \frac{\exp\{\boldsymbol{x}_{kij}\boldsymbol{\beta}_{kj} + \alpha_{ki}\}}{1 + \sum_{k=1}^{K-1} \exp\{\boldsymbol{x}_{kij}\boldsymbol{\beta}_{kj} + \alpha_{ki}\}}.$$

The likelihood for a random sample, and $\boldsymbol{\theta} = [\boldsymbol{\beta}, \rho, \sigma^2_{\alpha_1}, \sigma^2_{\alpha_1}]^\top$, is given by

$$L(\boldsymbol{\theta}; y) = \prod_{i=1}^{N} \int_{\Re} \int_{\Re} \prod_{j=1}^{n_i} \left[\binom{n_{ij}}{y_{1ij}, y_{2ij}, y_{3ij}} \prod_{k=1}^{K} p_{kij}^{y_{kij}} \right] \times \frac{\exp\left\{ -\frac{1}{2(1-\rho^2)} \left(\frac{\alpha^2_{1i}}{\sigma^2_{\alpha_1}} + \frac{\alpha^2_{2i}}{\sigma^2_{\alpha_2}} - \frac{2\alpha_{1i}\alpha_{2i}\rho}{\sigma_{\alpha_1}\sigma_{\alpha_2}} \right) \right\}}{2\pi\sigma_{\alpha_1}\sigma_{\alpha_2}\sqrt{1-\rho^2}} \, \mathrm{d}\alpha_{1i} \, \mathrm{d}\alpha_{2i}.$$

$$\text{i.e.,} \quad L(\boldsymbol{\theta}; y_i) = \int_{\Re} \int_{\Re} f(y_i \mid \alpha_{1i}, \alpha_{2i}) \, f(\alpha_{1i}, \alpha_{2i}) \, \mathrm{d}\alpha_{1i} \, \mathrm{d}\alpha_{2i}.$$

On the Agenda

1. Find the MLEs. Provide some confidence intervals.
2. Consider two covariates for each subject and propose a regression model.
3. Do the maximum likelihood estimation for the proposed model.
4. Do a simulation study to evaluate the MLEs distribution.
5. Evaluate the coverage rate for the Wald and deviance intervals.
6. Propose a mixed model for multiple observations from the same subject.
7. Do the maximum likelihood estimation for the proposed model.

First of all, let's simulate some data

```
data_setup <- function(N, n, k, rho, var1, var2) {
    gauss_dim <- k - 1 ; off_diag <- rho * sqrt(var1) * sqrt(var2)
    set.seed(1417)
    alpha <- rmvnorm(N, mean = rep(0, gauss_dim),
                     sigma = matrix(c(var1, rep(off_diag, 2), var2),
                                    gauss_dim, gauss_dim))
    data <- as.data.frame(
        matrix(0, nrow = N * n, ncol = 2 + k + gauss_dim))
    names(data) <- c("i", "j",
                     paste0("y", seq(k)), paste0("alpha", seq(gauss_dim)))
    data$i <- rep(seq(N), each = n) ; data$j <- rep(seq(n), N)
    for (i in seq(gauss_dim)) {
        data[ , paste0("alpha", i)] <- rep(alpha[ , i], each = n)}
    return(data)
}
N = 250 ; n = 10 ; k = 3 ## subjects, repeated measures and classes
bigdata <- data_setup(N, n, k, rho = - .25, var1 = .2, var2 = .4)
linear_pred <- list(y1 ~ 1, y2 ~ 1)
initial_values <- c("b01" = .85, "b02" = 1.25)
probs <- inv_logit(initial_values, linear_pred, bigdata)$ps
```

The data

```
set.seed(0040)
bigdata[ , paste0("y", seq(k))] <- rmultinomial(N * n, 1, prob = probs)
head(bigdata, 15)
```

```
##     i  j y1 y2 y3     alpha1     alpha2
## 1   1  1  0  0  1 -0.8283437 -0.9391010
## 2   1  2  0  1  0 -0.8283437 -0.9391010
## 3   1  3  0  1  0 -0.8283437 -0.9391010
## 4   1  4  0  0  1 -0.8283437 -0.9391010
## 5   1  5  0  1  0 -0.8283437 -0.9391010
## 6   1  6  0  0  1 -0.8283437 -0.9391010
## 7   1  7  0  1  0 -0.8283437 -0.9391010
## 8   1  8  1  0  0 -0.8283437 -0.9391010
## 9   1  9  1  0  0 -0.8283437 -0.9391010
## 10  1 10  0  0  1 -0.8283437 -0.9391010
## 11  2  1  0  1  0 -0.4822540 -0.8251952
## 12  2  2  0  1  0 -0.4822540 -0.8251952
## 13  2  3  0  1  0 -0.4822540 -0.8251952
## 14  2  4  1  0  0 -0.4822540 -0.8251952
## 15  2  5  1  0  0 -0.4822540 -0.8251952
```

Integrating into the random effects

```
library(tidyverse)
integrating <- function(alpha, beta, det_sigma, inv_sigma, preds, data) {
    ind_pred <- seq(preds) ; n_pred <- length(preds) ; k <- n_pred + 1
    beta <- split(beta, substr(names(beta), start = 3, stop = 3))
    list_X <- lapply(preds, model.matrix, data = data)
    exp_xb <- sapply(
        seq(list_X),
        function(i) exp(list_X[[i]] %*% beta[[i]] + alpha[i]))
    link_denominator <- 1 + rowSums(exp_xb)
    ps <- sapply(ind_pred, function(i) exp_xb[ , i]/link_denominator)
    ps <- cbind(ps, 1 - rowSums(ps)) ; colnames(ps) <- paste0("p", seq(k))
    y <- as.matrix(data[ , paste0("y", seq(k))]) ; n <- nrow(y)
    out <- sum(dmultinomial(y, size = 1, prob = ps, log = TRUE)) -
        (n/2) * log(2 * pi) -
        .5 * det_sigma - .5 * alpha %*% inv_sigma %*% alpha
    return(out) }
```

Ok, but how we integrate that?... Laplace approximation!

```
laplace <- function(lkl, dim, ...) {
    integral <- -6e+05
    initial <- numeric(dim)
    logQ <- try(optim(initial, lkl, ..., method = "BFGS",
                      control = list(fnscale = -1), hessian = TRUE),
                silent = TRUE)
    if (class(logQ) != "try-error") {
        integral <- logQ$value +
            (dim/2) * log(2*pi) - .5 * determinant(-logQ$hessian)$modulus
    }
    return(integral)
}
```

Now, we put everything together

```
multi_mixed <- function(theta, data, until) {
    out <- -sqrt(.Machine$double.xmax)
    beta <- theta[str_detect(names(theta), pattern = "^b\\d")]
    rho <- 2 * exp(theta["rho"])/(1 + exp(theta["rho"])) - 1
    var1 <- exp(theta["var1"]) ; var2 <- exp(theta["var2"])
    c1 <- 1 - rho^2 ; off_diag <- -rho/(sqrt(var1) * sqrt(var2) * c1)
    inv_sigma <-
        matrix(c(1/(var1 * c1), rep(off_diag, 2), 1/(var2 * c1)), 2, 2)
    det_sigma <- log(var1 * var2 * c1)[[1]]
    out <- future_map_dbl(
        seq(until),
        function(index) {
            laplace(lkl = integrating, dim = 2, beta = beta,
                    det_sigma = det_sigma, inv_sigma = inv_sigma,
                    preds = linear_pred,
                    data = data[data$i == index, ]) })
    return(-sum(out)) }
```

Let's see if all this stuff that I did really works

```
plan(multiprocess)
tic() ; mle2_fit <- mle2(
            multi_mixed, start = theta, method = "BFGS",
            data = list(data = bigdata[ , seq(5)], until = N)) ; toc()
```

```
## 751.249 sec elapsed
```

```
summary(mle2_fit)@coef
```

```
##        Estimate Std. Error    z value        Pr(z)
## b01   0.8748530 0.07302903 11.9795237 4.549299e-33
## b02   1.2174636 0.07441278 16.3609479 3.634265e-60
## rho   0.2380846 0.37685564  0.6317662 5.275397e-01
## var1 -1.3547682 0.45049568 -3.0072836 2.635938e-03
## var2 -0.9000712 0.27562542 -3.2655595 1.092481e-03
```

Compare!

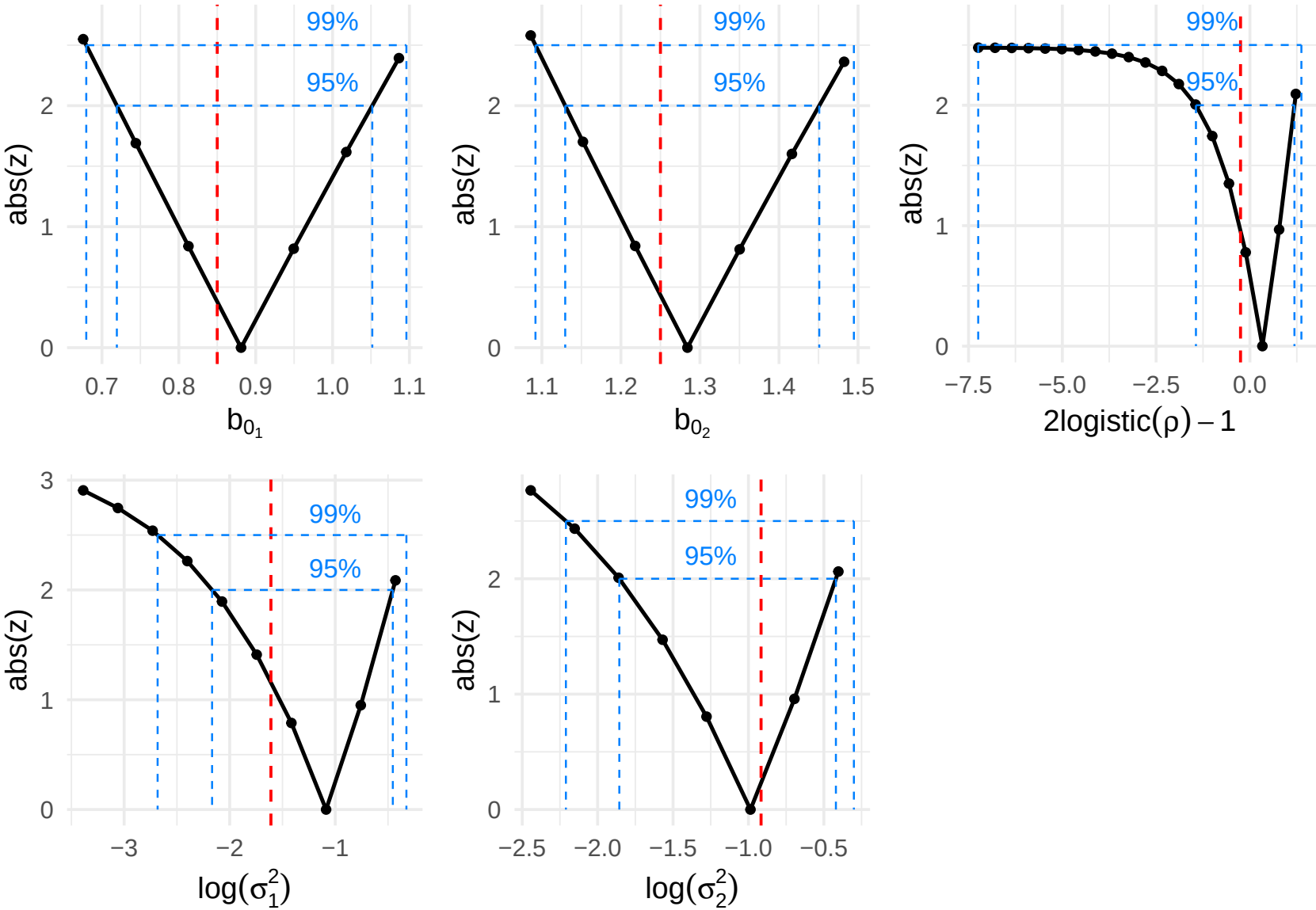
```
thetasss <- theta ; mle2_est <- mle2_fit@coef

mle2_est["rho"] <- 2 * exp(mle2_est["rho"])/(1 + exp(mle2_est["rho"])) - 1
thetasss[c("var1", "var2")] <- exp(thetasss[c("var1", "var2")])
mle2_est[c("var1", "var2")] <- exp(mle2_est[c("var1", "var2")])

rbind(thetasss, mle2_est)
```

```
##                b01      b02        rho      var1      var2
## thetasss 0.850000 1.250000 -0.2500000 0.2000000 0.4000000
## mle2_est 0.874853 1.217464  0.1184832 0.2580071 0.4065407
```

```
## standard errors
c(sqrt(diag(mle2_fit@vcov[1:2, 1:2])), delta_method)
```

```
##         b01         b02         rho        var1        var2
## 0.07302903 0.07441278 0.18578262 0.11623107 0.11205295
```

Profiling (and waiting 40828.454 sec)



Red dashed: true parameter value.

Next steps for Henrique of the near future

- Integrate the β's together with the random effects in the Laplace approximation;
- See how to get back the integrated β's, hahaha
- Change the `optim` routine inside the Laplace approx. by a Newton-Raphson algorithm;
- Check which parts of the code I can do in a faster way;
- More covariates and time-dependent covariates (β varying on time);
- Insert more dependency structures;
- Swim in Bayesian waters;
- Whatever else Wagner asks for hahaha
- ...

and. . .