Overview

When looking at bivariate binomial data with the aim of learning about the dependence that is present, possibly after correcting for some covariates many models are available.

- Random-effects models logistic regression covered elsewhere (glmer in lme4).
  
  in the mets package you can fit the

- Pairwise odds ratio model

- Bivariate Probit model
  - With random effects
  - Special functionality for polygenic random effects modelling such as ACE, ADE, AE and so forth.

- Additive gamma random effects model
  - Special functionality for polygenic random effects modelling such as ACE, ADE, AE and so forth.

Typically it can be hard or impossible to specify random effects models with special structure among the parameters of the random effects. This is possible in our models.

To be concrete about the model structure assume that we have paired binomial data $Y_1, Y_2, X_1, X_2$ where the responses are $Y_1, Y_2$ and we have covariates $X_1, X_2$.

We start by giving a brief description of these different models. First we for bivariate data one can specify the marginal probability using logistic regression models

$$\text{logit}(P(Y_i = 1|X_i)) = \alpha_i + X_i^T \beta_i = 1, 2.$$ 

These model can be estimated under working independence $^1$.

A typical twin analysis will typically consist of looking at both

- Pairwise odds ratio model

- Bivariate Probit model

The additive gamma can be used for the same as the bivariate probit model but is more restrictive in terms of dependence structure, but is nevertheless still valuable to have also as a check of results of the bivariate probit model.
Biprobit with random effects

For these model we assume that given random effects $Z$ and a covariate vector $V_{12}$ we have independent logistic regression models

$$\text{probit}(P(Y_i = 1|X_i, Z)) = \alpha_i + X_i^T \beta + V_{12}^T Z$$

where $Z$ is a bivariate normal distribution with some covariance $\Sigma$. The general covariance structure $\Sigma$ makes the model very flexible.

We note that

- Parameters $\beta$ are subject specific
- The $\Sigma$ will reflect dependence

The more standard link function logit rather than the probit link is often used and implemented in for example $^2$. The advantage is that one now gets an odds-ratio interpretation of the subject specific effects, but one then needs numerical integration to fit the model.

We note that

Pairwise odds ratio model

Now the pairwise odds ratio model the specifies that given $X_1, X_2$ the marginal models are

$$\text{logit}(P(Y_i = 1|X_i)) = \alpha_i + X_i^T \beta_i = 1, 2$$

The primary object of interest are the odds ratio between $Y_1$ and $Y_2$

$$\gamma_{12} = \frac{P(Y_{ki} = 1, Y_{kj} = 1)P(Y_{ki} = 0, Y_{kj} = 0)}{P(Y_{ki} = 1, Y_{kj} = 0)P(Y_{ki} = 0, Y_{kj} = 1)}$$

given $X_{ki}, X_{kj},$ and $Z_{kji}$. We model the odds ratio with the regression

$$\gamma_{12} = \exp(Z_{12}^T \lambda)$$

Where $Z_{12}$ are some covarites that may influence the odds-ratio between between $Y_1$ and $Y_2$ and contains the marginal covariates, $^3$. This odds-ratio is given covarites as well as marginal covariates. $^3, 1, 3$ and $^3, 1, 3$ and 3. The odds-ratio and marginals specify the joint bivariate distribution via the so-called Plackett-distribution.

One way of fitting this model is the ALR algorithm, the alternating logistic regression and this has been described in several papers $^4$. We here simply estimate the parameters in a two stage-procedure $^4, 1, 4$ and $^4, 1, 4$ and 4.

- Estimating the marginal parameters via GEE
- Using marginal estimates, estimate dependence parameters

This gives efficient estimates of the dependence parameters because of orthogonality, but some efficiency can be gained for the marginal parameters by using the full likelihood or iterative fitting such as for the ALR.

The pairwise odds-ratio model is very useful, but one do not have a random effects model.
Additive gamma model

Again we operate under marginal logistic regression models are

\[ \text{logit}(P(Y_i = 1|X_i)) = \alpha_i + X_i^T \beta_i = 1, 2 \]

First with just one random effect \( Z \) we assume that conditional on \( Z \) the responses are independent and follow the model

\[ \text{logit}(P(Y_i = 1|X_i, Z)) = \exp(-Z \cdot \Psi^{-1}(\lambda_\bullet, \lambda_\bullet, P(Y_i = 1|X_i))) \]

where \( \Psi \) is the laplace transform of \( Z \) where we assume that \( Z \) is gamma distributed with variance \( \lambda_\bullet^{-1} \) and mean 1. In general \( \Psi(\lambda_1, \lambda_2) \) is the laplace transform of a Gamma distributed random effect with \( Z \) with mean \( \lambda_1/\lambda_2 \) and variance \( \lambda_1/\lambda_2^2 \).

We fit this model by

- Estimating the marginal parameters via GEE
- Using marginal estimates, estimate dependence parameters

To deal with multiple random effects we consider random effects \( Z_i = 1, \ldots, d \) such that \( Z_i \) is gamma distributed with mean \( \lambda_j/\lambda_\bullet \) and variance \( \lambda_j/\lambda_\bullet^2 \), where we define the scalar \( \lambda_\bullet \) below.

Now given a cluster-specific design vector \( V_{12} \) we assume that

\[ V_{12}^T Z \]

is gamma distributed with mean 1 and variance \( \lambda_\bullet^{-1} \) such that critically the random effect variance is the same for all clusters. That is

\[ \lambda_\bullet = V_{12}^T (\lambda_1, \ldots, \lambda_d) \]

We return to some specific models below, and show how to fit the ACE and AE model using this set-up.

One last option in the model-specification is to specify how the parameters \( \lambda_1, \ldots, \lambda_d \) are related. We thus can specify a matrix \( M \) of dimension \( p \times d \) such that

\[ (\lambda_1, \ldots, \lambda_d)^T = M \theta \]

where \( \theta \) is \( d \)-dimensional. If \( M \) is diagonal we have no restrictions on parameters.

This parametrization is obtained with the var.par=0 option that thus estimates \( \theta \).

The DEF AULT parametrization instead estimates the variances of the random effects (var.par=1) via the parameters \( \nu \)

\[ M \nu = (\lambda_1/\lambda_\bullet^2, \ldots, \lambda_d/\lambda_\bullet^2)^T \]

The basic modelling assumption is now that given random effects \( Z = (Z_1, \ldots, Z_d) \) we have independent probabilites

\[ \text{logit}(P(Y_i = 1|X_i, Z)) = \exp(-V_{12,i}^T Z \cdot \Psi^{-1}(\lambda_\bullet, \lambda_\bullet, P(Y_i = 1|X_i))) i = 1, 2 \]

We fit this model by
Estimating the marginal parameters via GEE

Using marginal estimates, estimate dependence parameters

Even though the model not formally in this formulation allows negative correlation in practice the parameters can be negative and this reflects negative correlation. An advantage is that no numerical integration is needed.

**The twin-stutter data**

We consider the twin-stutter where for pairs of twins that are either dizygotic or monozygotic we have recorded whether the twins are stuttering. We here consider MZ and same sex DZ twins.

Looking at the data

```r
library(mets)
data(twinstut)
twinstut$binstut <- 1*(twinstut$stutter=="yes")
twinsall <- twinstut	winstut <- subset(twinstut, zyg%in%c("mz", "dz"))
head(twinstut)
```

```
Loading required package: timereg
Loading required package: survival
lava version 1.5.1
mets version 1.2.1.2
Attaching package: 'mets'
The following object is masked _by_ '.GlobalEnv':
object.defined
Warning message:
failed to assign RegisteredSymbol for cor to cor since cor is already defined in the 'mets' namespace
tvparsnr zyg stutter sex age nr binstut
1 2001005 mz no female 71 1 0
2 2001005 mz no female 71 2 0
3 2001006 dz no female 71 1 0
8 2001012 mz no female 71 1 0
9 2001012 mz no female 71 2 0
11 2001015 dz no male 71 1 0
```

**Pairwise odds ratio model**

We start by fitting an overall dependence OR for both MZ and DZ even though the dependence is expected to be different across zygosities.

The first step is to fit the marginal model adjusting for marginal covariates. We here note that there is a rather strong gender effect in the risk of stuttering.

```r
margbin <- glm(binstut~factor(sex)+age, data=twinstut, family=binomial())
summary(margbin)
```
Call:
glm(formula = binstut ~ factor(sex) + age, family = binomial(),
data = twinstut)

Deviance Residuals:
   Min      1Q  Median      3Q     Max
-0.4419  -0.4078  -0.2842  -0.2672   2.6395

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.027625   0.104012 -29.108  < 2e-16 ***
factor(sex)male  0.869826   0.062197  13.985  < 2e-16 ***
age            -0.005983   0.002172  -2.754   0.00588 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 9328.6 on 21287 degrees of freedom
Residual deviance: 9117.0 on 21285 degrees of freedom
AIC: 9123

Number of Fisher Scoring iterations: 6

Now estimating the OR parameter. We see a strong dependence with an OR at around 8 that is clearly significant.

Now, and more interestingly, we consider an OR that depends on zygosity and note that MZ have a much larger OR than DZ twins. This type of trait is somewhat complicated to interpret, but clearly, one option is that that there is a genetic effect, alternatively there might be a stronger environmental effect for MZ twins.
We now consider further regression modelling of the OR structure by considering possible interactions between sex and zygozsity. We see that MZ has a much higher dependence and that males have a much lower dependence. We tested for interaction in this model and these were not significant.

```r
theta <- scale(twinstut$age)
theta.des <- model.matrix( ~-1+factor(zyg)+factor(sex),data=twinstut)
bina <- binomial.twostage(margbin,data=twinstut,var.link=1,
clusters=twinstut$tvparnr,theta.des=theta.des)
summary(bina)
```

Dependence parameter for Odds-Ratio (Plackett) model
With log-link
$estimates
theta   se
factor(zyg)dz  0.5221651 0.2401355
factor(zyg)mz  3.4853933 0.1866076

$or
Estimate Std.Err 2.5% 97.5% P-value
factor(zyg)dz  1.69 0.405 0.892 2.48 3.12e-05
factor(zyg)mz  32.64 6.090 20.699 44.57 8.38e-08

$type
[1] "plackett"
attr(,"class")
[1] "summary.mets.twostage"

 Alternative syntax

We now demonstrate how the models can fitted jointly and with another syntax, that of course just fits the marginal model and subsequently fits the pairwise OR model.

First noticing as before that MZ twins have a much higher dependence.

```r
# refers to zygosity of first subject in each pair : zyg1
# could also use zyg2 (since zyg2=zyg1 within twinpair's)
out <- easy.binomial.twostage(stutter~factor(sex)+age,data=twinstut,
clusters=twinstut$tvparnr,theta.des=theta.des)
```
response="binstut",id="tvparnr",var.link=1,
theta.formula=-1+factor(zyg1))

summary(out)

Dependence parameter for Odds-Ratio (Plackett) model
With log-link
$estimates
theta se
factor(zyg1)dz 0.5221651 0.2401355
factor(zyg1)mz 3.4853933 0.1866076

$or
Estimate Std.Err 2.5% 97.5% P-value
factor(zyg1)dz 1.69 0.405 0.892 2.48 3.12e-05
factor(zyg1)mz 32.64 6.090 20.699 44.57 8.38e-08

$type
[1] "plackett"
attr(,"class")
[1] "summary.mets.twostage"

Now considering all data and estimating separate effects for the OR for opposite sex DZ twins and same sex twins. We here find that os twins are not markedly different from the same sex DZ twins.

# refers to zygosity of first subject in each pair : zyg1
# could also use zyg2 (since zyg2=zyg1 within twinpair's)

desfs<-function(x,num1="zyg1",num2="zyg2")
c(x[num1]=="dz",x[num1]=="mz",x[num1]=="os")*1

margbinall <- glm(binstut~factor(sex)+age,data=twinsall,
family=binomial())
out3 <- easy.binomial.twostage(binstut~factor(sex)+age,
data=twinsall,response="binstut",id="tvparnr",var.link
=1,
theta.formula=desfs,desnames=c("dz","mz","os"))

summary(out3)

Dependence parameter for Odds-Ratio (Plackett) model
With log-link
$estimates
theta se
dz 0.5278527 0.2396796
mz 3.4853933 0.1866076
os 0.7802940 0.2894394

$or
Estimate Std.Err 2.5% 97.5% P-value
dz 1.70 0.406 0.899 2.49 3.02e-05
mz 32.62 6.081 20.703 44.54 8.13e-08
os 2.18 0.632 0.944 3.42 5.50e-04

$type
[1] "plackett"
attr(,"class")
[1] "summary.mets.twostage"
library(mets)
data(twinstut)
twinstut <- subset(twinstut, zyg%in%c("mz","dz"))
twinstut$binstut <- 1*(twinstut$stutter=="yes")
head(twinstut)

Bivariate Probit model

First testing for same dependence in MZ and DZ that we recommend doing by comparing the correlations of MZ and DZ twins. Apart from regression correction in the mean this is an un-structured model, and the useful concordance and casewise concordance estimates can be reported from this analysis.

b1 <- bptwin(binstut~sex, data=twinstut, id="tvparnr", zyg="zyg", DZ="dz", type="un")
summary(b1)

Polygenic modelling

We now turn attention to specific polygenic modelling where special random effects are used to specify ACE, AE, ADE models and
so forth. This is very easy with the bptwin function. The key parts of the output are the sizes of the genetic component A and the environmental component, and we can compare with the results of the unstructured model above. Also formally we can test if this sub-model is acceptable by a likelihood ratio test.

1
b1 <- bptwin(binstut~sex,data=twinstut,id="tvparnr",zyg="zyg",DZ="dz",type="ace")

2
summary(b1)

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Std.Err</th>
<th>Z</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-3.70371</td>
<td>0.24449</td>
<td>-15.14855</td>
</tr>
<tr>
<td>sexmale</td>
<td>0.83310</td>
<td>0.08255</td>
<td>10.09201</td>
</tr>
<tr>
<td>log(var(A))</td>
<td>1.18278</td>
<td>0.17179</td>
<td>6.88512</td>
</tr>
<tr>
<td>log(var(C))</td>
<td>-29.99519</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Total MZ/DZ Complete pairs MZ/DZ
8777/12511 3255/4058

<table>
<thead>
<tr>
<th>Estimate</th>
<th>2.5%</th>
<th>97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.76545</td>
<td>0.70500</td>
</tr>
<tr>
<td>C</td>
<td>0.00000</td>
<td>0.00000</td>
</tr>
<tr>
<td>E</td>
<td>0.23455</td>
<td>0.17410</td>
</tr>
<tr>
<td>MZ Tetrachoric Cor</td>
<td>0.76545</td>
<td>0.69793</td>
</tr>
<tr>
<td>DZ Tetrachoric Cor</td>
<td>0.38272</td>
<td>0.35210</td>
</tr>
</tbody>
</table>

MZ:

<table>
<thead>
<tr>
<th>Estimate</th>
<th>2.5%</th>
<th>97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordance</td>
<td>0.01560</td>
<td>0.01273</td>
</tr>
<tr>
<td>Casewise Concordance</td>
<td>0.42830</td>
<td>0.36248</td>
</tr>
<tr>
<td>Marginal</td>
<td>0.03643</td>
<td>0.03294</td>
</tr>
<tr>
<td>log(OR)</td>
<td>3.52382</td>
<td>3.13466</td>
</tr>
</tbody>
</table>

DZ:

<table>
<thead>
<tr>
<th>Estimate</th>
<th>2.5%</th>
<th>97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordance</td>
<td>0.00558</td>
<td>0.00465</td>
</tr>
<tr>
<td>Casewise Concordance</td>
<td>0.15327</td>
<td>0.13749</td>
</tr>
<tr>
<td>Marginal</td>
<td>0.03643</td>
<td>0.03294</td>
</tr>
<tr>
<td>Rel.Recur.Risk</td>
<td>4.20744</td>
<td>3.78588</td>
</tr>
<tr>
<td>log(OR)</td>
<td>1.69996</td>
<td>1.57262</td>
</tr>
</tbody>
</table>

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<tr>
<th>Estimate</th>
<th>2.5%</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Broad-sense heritability</td>
<td>0.76545</td>
<td>0.70500</td>
</tr>
</tbody>
</table>

2
b0 <- bptwin(binstut~sex,data=twinstut,id="tvparnr",zyg="zyg",DZ="dz",type="ae")

3
summary(b0)

<table>
<thead>
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<td>1.18278</td>
<td>0.17179</td>
<td>6.88512</td>
</tr>
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</table>

Total MZ/DZ Complete pairs MZ/DZ
8777/12511 3255/4058

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<td>0.17410</td>
</tr>
<tr>
<td>MZ Tetrachoric Cor</td>
<td>0.76545</td>
<td>0.69793</td>
</tr>
</tbody>
</table>
Additive gamma random effects

Fitting first a model with different size random effects for MZ and DZ. We note that as before in the OR and biprobit model the dependence is much stronger for MZ twins. We also test if these are the same by parametrizing the OR model with an intercept. This clearly shows a significant difference.

```
theta.des <- model.matrix(~-1+factor(zyg),data=twinstut)
margbin <- glm(binstut~sex,data=twinstut,family=binomial())
bintwin <- binomial.twostage(margbin,data=twinstut,model="gamma",
  clusters=twinstut$tvparnr,detail=0,theta=c(0.1)/1, var. link=1,
  theta.des=theta.des)
summary(bintwin)

# test for same dependence in MZ and DZ
theta.des <- model.matrix(~factor(zyg),data=twinstut)
margbin <- glm(binstut~sex,data=twinstut,family=binomial())
bintwin <- binomial.twostage(margbin,data=twinstut,model="gamma",
  clusters=twinstut$tvparnr,detail=0,theta=c(0.1)/1, var. link=1,
  theta.des=theta.des)
summary(bintwin)
```

Dependence parameter for Clayton-Oakes model

Variance of Gamma distributed random effects

With log-link

$estimates

<table>
<thead>
<tr>
<th>theta</th>
<th>se</th>
</tr>
</thead>
<tbody>
<tr>
<td>factor(zyg)dz</td>
<td>-2.61194495 0.4854454</td>
</tr>
<tr>
<td>factor(zyg)mz</td>
<td>-0.01817181 0.1030735</td>
</tr>
</tbody>
</table>

$vargam

<table>
<thead>
<tr>
<th>Estimate Std.Err</th>
<th>2.5%</th>
<th>97.5%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>factor(zyg)dz</td>
<td>0.0734 0.0356 0.00356 0.143 3.94e-02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>factor(zyg)mz</td>
<td>0.9820 0.1012 0.78361 1.180 2.96e-22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Polygenic modelling

First setting up the random effects design for the random effects and the relationship between variance parameters. We see that the genetic random effect has size one for MZ and 0.5 for DZ subjects, that have shared and non-shared genetic components with variance 0.5 such that the total genetic variance is the same for all subjects. The shared environmental effect is the same for all. Thus two parameters with these bands.

```r
out <- twin.polygen.design(twinstut,id="tvparnr",zygname="zyg",zyg="dz",type="ace")
head(cbind(out$des.rv,twinstut$tvparnr),10)
```

```
[1,] 1.0 0.0 0.0 0.0 1.0
[2,] 0.5 0.0 0.0 0.0 0.5
[3,] 0.5 0.0 0.0 0.0 0.5
[4,] 0.0 1.0 0.0 0.0 0.0
```

Now, fitting the ACE model, we see that the variance of the genetic component is 1.5 and the environmental variance is -0.5. Thus suggesting that the ACE model does not fit the data. When the random design is given we automatically use the gamma frailty model.
margbin <- glm(binstut~sex,data=twinstut,family=binomial())
bintwin1 <- binomial.twostage(margbin,data=twinstut,
    clusters=twinstut$tvparnr,detail=0,theta=c(0.1)/1,var.
    link=0,
    random.design=out$des.rv,theta.des=out$pardes)
summary(bintwin1)

Dependence parameter for Clayton-Oakes model
Variance of Gamma distributed random effects
$estimates
  theta  se
dependence1  1.5261839 0.2475041
dependence2 -0.5447955 0.1942159

$type
[1] "clayton.oakes"
$h
  Estimate Std.Err 2.5% 97.5% P-value
dependence1  1.555 0.187 1.189 1.922 9.11e-17
dependence2 -0.555 0.187 -0.922 -0.189 2.99e-03
$vare
NULL
$vartot
  Estimate Std.Err 2.5% 97.5% P-value
p1 0.981 0.102 0.781 1.18 8.29e-22
attr("class")
[1] "summary.mets.twostage"

For this model we estimate the concordance and casewise concordance as well as the marginal rates of stuttering for females.

concordanceTwinACE(bintwin1,type="ace")

$MZ
  Estimate Std.Err 2.5% 97.5% P-value
concordance  0.0182 0.00147 0.0153 0.0211 2.61e-35
casewise concordance  0.5033 0.03266 0.4395 0.5672 6.49e-54
marginal  0.0362 0.00188 0.0325 0.0399 7.15e-83

$DZ
  Estimate Std.Err 2.5% 97.5% P-value
concordance  0.00235 0.000589 0.0012 0.00351 6.45e-05
casewise concordance  0.06501 0.015836 0.0340 0.09604 4.04e-05
marginal  0.03620 0.001877 0.0325 0.03988 7.15e-83

The E component was not consistent with the fit of the data and we now consider instead the AE model.

out <- twin.polygen.design(twinstut,id="tvparnr",zygname="
zyg",zyg="dz",type="ae")
bintwin <- binomial.twostage(margbin,data=twinstut,
    clusters=twinstut$tvparnr,detail=0,theta=c(0.1)/1,var.
    link=0,
    random.design=out$des.rv,theta.des=out$pardes)
summary(bintwin)
Dependence parameter for Clayton-Oakes model
Variance of Gamma distributed random effects
$estimates
  theta  se
dependence1  0.9094847 0.09536288
$type
[1] "clayton.oakes"
$h
  Estimate Std.Err 2.5% 97.5% P-value
dependence1 1 0 1 1 0
$vare
NULL
$vartot
  Estimate Std.Err 2.5% 97.5% P-value
p1  0.909 0.0954 0.723 1.1 1.47e-21
attr(,"class")
[1] "summary.mets.twostage"

Again, the concordance can be computed:

: concordanceTwinACE(bintwin,type="ae")

$MZ
  Estimate Std.Err 2.5% 97.5% P-value
concordance 0.0174 0.00143 0.0146 0.0202 5.00e-34
casewise concordance 0.4795 0.03272 0.4154 0.5437 1.20e-48
marginal 0.0362 0.00188 0.0325 0.0399 7.15e-83

$DZ
  Estimate Std.Err 2.5% 97.5% P-value
concordance 0.00477 0.000393 0.0040 0.00554 5.94e-34
casewise concordance 0.13175 0.005417 0.1211 0.14237 1.14e-130
marginal 0.03620 0.001877 0.0325 0.03988 7.15e-83