

Additive Genetic Models in Mixed Populations

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Contents

Full diallel trial with founders from two different base populations E and J

```
## Setup
library(breedR)
library(ggplot2)
set.seed(123)

## Simulation parameters
n.founders <- c(E = 9, J = 9)
sigma2 <- c(E = 3, J = 2, resid = 1)

founders <- data.frame(id = c(paste0('E', 1:n.founders['E']),
                             paste0('J', 1:n.founders['J'])),
                      pop.idx = c(rep(1, n.founders['E']),
                                rep(2, n.founders['J'])),
                      BV = c(rnorm(n.founders['E'], sd = sqrt(sigma2['E'])),
                            rnorm(n.founders['J'], sd = sqrt(sigma2['J']))))

n.obs <- sum(n.founders)*150
obs.parents.idx <- matrix(sample(nrow(founders), 2*n.obs, replace = TRUE), ncol = 2)

## The 'family' is independent of the order of the parents
## While the population only takes into account the origin
## e.g. cross2fam(c('J3', 'E1')) gives 'E1:J3'
## while cross2pop(c('J3', 'E1')) gives 'EJ'
cross2fam <- function(x) paste(founders$id[sort(x)], collapse = ':')
cross2pop <- function(x) paste(names(n.founders)[founders$pop.idx[sort(x)]], collapse = '')

## Mendelian sampling term
msp <- function(x) {
  ss <- sigma2[founders$pop.idx[x]]
  s2 <- (ss[1] + ss[2])/4
  rnorm(1, sd = sqrt(s2))
}

dat <- data.frame(
  id = sum(n.founders) + seq.int(n.obs),
  dad = obs.parents.idx[, 1],
  mum = obs.parents.idx[, 2],
  fam = apply(obs.parents.idx, 1, cross2fam),
  sp = apply(obs.parents.idx, 1, cross2pop),
  bv = apply(obs.parents.idx, 1,
             function(x) mean(founders$BV[x]) + msp(x)),
```

```

resid = rnorm(n.obs, sd = sqrt(sigma2['resid']))

dat <- transform(dat,
                 y = bv + resid)

## Printing simulated setting
print(table(dat[, c('mum', 'dad')]), zero.print = "")

```

```

##      dad
## mum   1  2  3  4  5  6  7  8  9 10 11 12 13 14 15 16 17 18
##  1    9  7  8 11 14  5 10 13  7  5  6 11  6 11 12  7 11 11
##  2    5  7 10  6  7  6  6  6  6 10  8 10  8  9  6  9  6  9
##  3   10  5 16 11 11  9  7 13 12  5  9 10  9  3 10  8  5 13
##  4    9  8  8  3  9  6  4  4  7  9 12 10  2  9 10 16  5  7
##  5    6  6  6  5  8  7 10 10 12  8  9  9  9  9  5 11  6  7
##  6    9 12  9  9 10  3 11 11 11 11  8 10  7 10  9  7 14  6
##  7   11  6  7 10  6 12  6  8  6  7 11  7  6  5 10  9  8  8
##  8    8 13 13  5  9 14 11 10  8  6 10  9  8  5 11  9  4  9
##  9    6  9  7  7  7  8 10  9 12  6  6  7  8 14  7  5  8  4
## 10   10  2  8  5  8 10 12  9 14  7 10  5 10  6 11  5  4  4
## 11   10  6  5  5 15  9  9 12  9 12  5  9  8 12  8  6  9  9
## 12   10  7  4  9  4  2  8 10  7  4  9 15 10  7 10 10  9  5
## 13  11 10  8  5 12  9  6 11 15 10 14 10  3  9  7  6  6 12
## 14   8 14  7 12 12 13  6  5 11  8  2  5  8 10  5 12  5  5
## 15  12  7 14  5  5 11  3  8 10  8  9 13  9  8  9  9  7 13
## 16  10 15 11  8  7  4  7 10  9  6  8  7  9 12  8  6  5 14
## 17   8  5 12 14  5 13  1  8  7  8  6  7  7  9 10  5  8 10
## 18   5  6 15  9 10  2  8  1  6  8  6 10  5  5 12 13  7  6

```

```
str(dat)
```

```

## 'data.frame': 2700 obs. of 8 variables:
## $ id : num 19 20 21 22 23 24 25 26 27 28 ...
## $ dad : int 14 4 6 5 3 8 8 7 3 3 ...
## $ mum : int 13 14 13 16 6 4 2 1 17 15 ...
## $ fam : Factor w/ 171 levels "E1:E1","E1:E2",...: 152 62 88 78 39 56 25 7 50 48 ...
## $ sp : Factor w/ 3 levels "EE","EJ","JJ": 3 2 2 2 1 1 1 1 2 2 ...
## $ bv : num 1.837 -0.585 3.279 2.039 1.376 ...
## $ resid: num 2.234 -0.672 -1.495 -0.133 1.17 ...
## $ y : num 4.07 -1.26 1.78 1.91 2.55 ...

```

There will be two independent additive-genetic variance models for the J and E populations. Each variance component will be estimated using the *pure* offspring only.

```

## Build a pedigree for the whole mixed population
## and get the kinship matrix A
ped <- build_pedigree(1:3, data = dat)
A <- pedigreemm::getA(ped)

## Build the full incidence matrix
Z <- as(dat$id, 'indMatrix')

```

0.1 Method 1: Hybrids as an independent population

This is the easiest way to go. It works as a first approximation, but has several shortcomings.

It needs to estimate one *virtual* variance for the hybrid population which is not linked to any genetic variance in the *real world*. Moreover, we don't use the hybrid observations to learn about the two variances that really matter: σ^2_E and σ^2_J

The advantage is that it predicts the Breeding Values of the hybrid offspring. However, the accuracy may be limited by the violation of the *single population* hypothesis of the model.

```
## Avoid estimating BLUPS for which we don't have information
## Otherwise, the run takes much longer (5 hs vs 6 min in this example)

## Give the index vector of additive-genetic random effects
## that belong to one subpopulation;
## 'E', 'J' (founders) or 'EE', 'EJ' or 'JJ' (offspring).
idx_pop <- function(x) {
  if (nchar(x) == 1) grep(x, founders$id)
  else
    match(dat$id[dat$sp == x], as.data.frame(ped)$self)
}

## A[idx_pop('EE'), idx_pop('JJ')] # This is null: populations are independent
Z_EE <- Z[, idx_pop('EE')]
Z_EJ <- Z[, idx_pop('EJ')]
Z_JJ <- Z[, idx_pop('JJ')]

A_EE <- A[idx_pop('EE'), idx_pop('EE')]
A_EJ <- A[idx_pop('EJ'), idx_pop('EJ')]
A_JJ <- A[idx_pop('JJ'), idx_pop('JJ')]

## Now fit a model with three additive-genetic components,
## by means of generic effects (as only one 'genetic' is allowed in breedR)

res1 <- remlf90(y ~ sp,
  generic = list(
    E = list(incidence = Z_EE,
              covariance = A_EE),
    J = list(incidence = Z_JJ,
              covariance = A_JJ),
    H = list(incidence = Z_EJ,
              covariance = A_EJ)),
  data = dat
)
```

```
## Warning in remlf90(y ~ sp, generic = list(E = list(incidence = Z_EE, covariance = A_EE), : No specific
##      Using default value of 1 for all variance components.
##      See ?breedR.getOption.
```

```
summary(res1)
```

```
## Linear Mixed Model with pedigree and spatial effects fit by AI-REMLF90 ver. 1.110
##      Data: dat
```

```
##      AIC      BIC logLik
## 10067 10091 -5029
##
## Variance components:
##      Estimated variances   S.E.
## E                3.414 0.7079
## J                2.213 0.6757
## H                2.466 0.6606
## Residual          1.004 0.3316
##
## Fixed effects:
##      value    s.e.
## sp.EE 0.21488 0.6192
## sp.EJ 0.24748 0.3724
## sp.JJ 0.15989 0.4992

PBV <- as.matrix(cbind(Z_EE, Z_JJ, Z_EJ)) %*%
  do.call('rbind', lapply(ranef(res1), function(x) cbind(PBV = x, se = attr(x, 'se'))))

ggplot(cbind(dat, PBV), aes(bv, PBV)) +
  geom_point() +
  geom_abline(int = 0, sl = 1, col = 'darkgray')
```

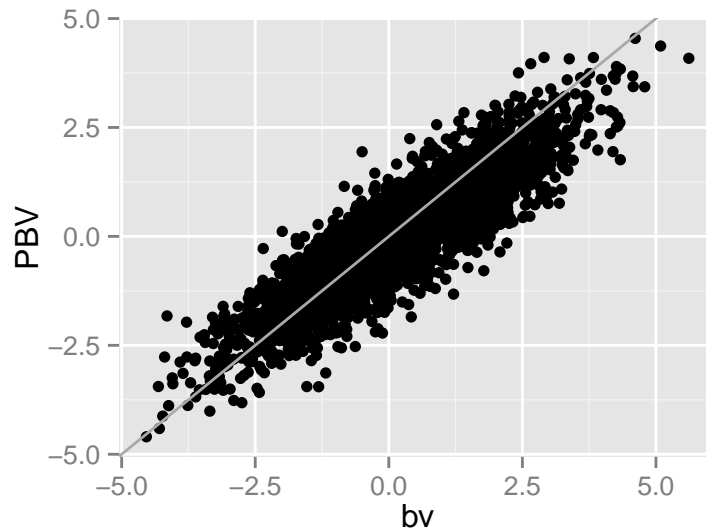


Figure 1:

0.2 Method 2: GCA/SCA model for hybrids

Another approach is to model hybrids with GCAs and SCAs, with additional variance parameters. The additive component of the genetic variances for the E and J populations is half the population variance. But these parameters will also gather dominance and epistasis effects.

However, we don't take advantage of the known relationship between the additive components by treating them as independent parameters. Furthermore, we don't use the relationship between hybrids and pures to learn about the original genetic variances. Nor even within hybrids, as we treat SCA as an unstructured effect, while there are both half and full siblings.

```

## We only want to apply 'dad', 'mum' and 'sca' effects to hybrids,
## and make it zero for non-hybrids. We do so by pre-multiplying by a
## diagonal indicator matrix
Ind <- diag(dat$sp == 'EJ')

## Build a specific incidence matrices for generic random effects
Z_dad <- Ind %*% as(dat$dad, 'indMatrix')
Z_mum <- Ind %*% as(dat$mum, 'indMatrix')
Z_sca <- Ind %*% as(as.numeric(dat$fam), 'indMatrix')

## The structure variances are diagonal
D <- diag(sum(n(founders)))

res2 <- remlf90(y ~ sp,
               generic = list(
                 E = list(incidence = Z_EE,
                           covariance = A_EE),
                 J = list(incidence = Z_JJ,
                           covariance = A_JJ),
                 dad = list(incidence = Z_dad,
                             covariance = D),
                 mum = list(incidence = Z_mum,
                             covariance = D),
                 sca = list(incidence = Z_sca,
                             covariance = diag(nlevels(dat$fam)))),
               data = transform(dat)
)

```

```

## Warning in remlf90(y ~ sp, generic = list(E = list(incidence = Z_EE, covariance = A_EE), : No specif
##      Using default value of 1 for all variance components.
##      See ?breedR.getOption.

```

```
summary(res2)
```

```

## Linear Mixed Model with pedigree and spatial effects fit by AI-REMLF90 ver. 1.110
##      Data: transform(dat)
##      AIC      BIC logLik
## 10137 10172 -5062
##
## Variance components:
##      Estimated variances      S.E.
## E              1.52350 0.29447
## J              0.73817 0.19334
## dad            0.66033 0.24008
## mum            0.55015 0.20263
## sca            0.01581 0.02514
## Residual       2.07940 0.07179
##
## Fixed effects:
##      value      s.e.
## sp.EE 0.21521 0.4165
## sp.EJ 0.25605 0.2627
## sp.JJ 0.15932 0.2929

```

```
PBV <- as.matrix(cbind(Z_EE, Z_JJ, Z_dad, Z_mum, Z_sca)) %*%
do.call('rbind', lapply(ranef(res2), function(x) cbind(PBV = x, se = attr(x, 'se'))))

ggplot(cbind(dat, PBV), aes(bv, PBV)) +
  geom_point() +
  geom_abline(int = 0, sl = 1, col = 'darkgray')
```

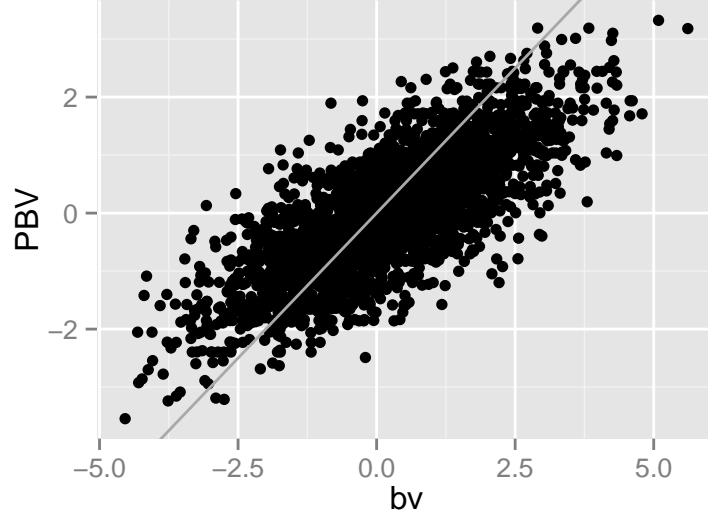


Figure 2:

This approach does not work very well. Much of the variation has not been adequately accounted for, and ended up in the residuals. May be there is some misspecification in the model.

0.3 Method 3: grid search

The difficulty of the problem resides that we cannot estimate two variance parameters at the same time. If we split the matrix A in blocks corresponding to each subpopulation, we can write the covariance matrix for the mixture as

$$\begin{aligned} \Sigma &= \begin{bmatrix} \sigma_E^2 A_E & \mathbf{0} & \sigma_E^2 A_{E:EE} & \frac{3\sigma_E^2 + \sigma_J^2}{4} A_{E:H} & \mathbf{0} \\ \mathbf{0} & \sigma_J^2 A_J & \mathbf{0} & \frac{\sigma_E^2 + 3\sigma_J^2}{4} A_{J:H} & \sigma_J^2 A_{J:JJ} \\ \sigma_E^2 A_{E:EE} & \mathbf{0} & \sigma_E^2 A_{EE} & \frac{3\sigma_E^2 + \sigma_J^2}{4} A_{EH} & \mathbf{0} \\ \frac{3\sigma_E^2 + \sigma_J^2}{4} A_{E:H} & \frac{\sigma_E^2 + 3\sigma_J^2}{4} A_{J:H} & \frac{3\sigma_E^2 + \sigma_J^2}{4} A_{HE} & \frac{\sigma_E^2 + \sigma_J^2}{2} A_{HH} & \frac{\sigma_E^2 + 3\sigma_J^2}{4} A_{HJ} \\ \mathbf{0} & \sigma_J^2 A_{J:JJ} & \mathbf{0} & \frac{\sigma_E^2 + 3\sigma_J^2}{4} A_{JH} & \sigma_J^2 A_{JJ} \end{bmatrix} \\ &= \sigma_E^2 \begin{bmatrix} A_E & \mathbf{0} & A_{E:EE} & \frac{3+\lambda}{4} A_{E:H} & \mathbf{0} \\ \mathbf{0} & \lambda A_J & \mathbf{0} & \frac{1+3\lambda}{4} A_{J:H} & \lambda A_{J:JJ} \\ A_{E:EE} & \mathbf{0} & A_{EE} & \frac{3+\lambda}{4} A_{EH} & \mathbf{0} \\ \frac{3+\lambda}{4} A_{E:H} & \frac{1+3\lambda}{4} A_{J:H} & \frac{3+\lambda}{4} A_{HE} & \frac{1+\lambda}{2} A_{HH} & \frac{1+3\lambda}{4} A_{HJ} \\ \mathbf{0} & \lambda A_{J:JJ} & \mathbf{0} & \frac{1+3\lambda}{4} A_{JH} & \lambda A_{JJ} \end{bmatrix}, \end{aligned} \quad (1)$$

where $\lambda = \frac{\sigma_J^2}{\sigma_E^2}$.

However, if we are not interested in evaluating the parents, we can disregard the first two block rows and columns from the matrix.

Now, fit the model for several values of λ and maximize the likelihood.

```
## Setup parallel computing
library(doParallel)
cl <- makeCluster(8)
registerDoParallel(cl)

## Introduce the corresponding scaling factors
## in the relationship matrix
scale_A <- function(x) {

  ## The pure E subpopulations remains the same
  S <- A
  E.idx <- c(idx_pop('E'), idx_pop('EE'))

  ## The pure J subpopulations get multiplied by lambda
  J.idx <- c(idx_pop('J'), idx_pop('JJ'))
  S[J.idx, J.idx] <- A[J.idx, J.idx] * x

  ## The hybrids related wuth pure E get a factor of (3+lambda)/4
  S[idx_pop('EJ'), E.idx] <- A[idx_pop('EJ'), E.idx] * (3+x)/4
  S[E.idx, idx_pop('EJ')] <- A[E.idx, idx_pop('EJ')] * (3+x)/4

  ## The hybrids related wuth pure J get a factor of (1+3*lambda)/4
  S[idx_pop('EJ'), J.idx] <- A[idx_pop('EJ'), J.idx] * (1+3*x)/4
  S[J.idx, idx_pop('EJ')] <- A[J.idx, idx_pop('EJ')] * (1+3*x)/4

  ## Finally, the hybrids related with other hybrids get a factor of (1+lambda)/2
  S[idx_pop('EJ'), idx_pop('EJ')] <- A[idx_pop('EJ'), idx_pop('EJ')] * (1+x)/2

  return(S)
}

## Conditional likelihood given lambda
cond_lik <- function(x) {
  require(breedR)
  ## Conditional structure matrix
  S <- scale_A(x)

  ## Temporarily, let's use only the pure pops
  idx <- c(idx_pop('EE'), idx_pop('JJ'))

  suppressWarnings(
    res <- remlf90(y ~ sp,
      generic = list(
        E = list(incidence = Z[dat$sp != 'EJ', idx],
          covariance = S[idx, idx])),
        data = dat[dat$sp != 'EJ', ]
      )
    )
  logLik(res)
}

lambda <- seq(.3, 1, length.out = 11)
```

```
# lik <- sapply(lambda, cond_lik) # (sequential)
lik <- foreach(x = seq.int(lambda), .combine = c) %dopar% cond_lik(lambda[x])

ggplot(data.frame(lambda, lik), aes(lambda, lik)) +
  geom_line()
```

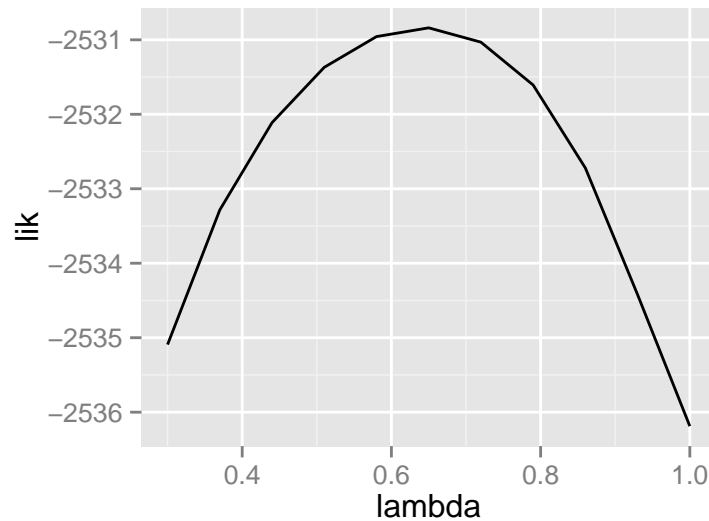


Figure 3:

This one works well. But for some reason, when I include the hybrids, for lambdas below about 0.58 and all the variance is accounted for residual variance.

There must be something wrong somewhere. May be the simulation of the Breeding Values is not correct?

Analogously, if I include only the hybrid subpopulation, it also works quite well, identifying the base variance.

```
## Take lambda maximizing the likelihood
lambda0 <- lambda[which.max(lik)]

S <- scale_A(lambda0)

## Temporarily, let's use only the pure pops
idx <- c(idx_pop('EE'), idx_pop('JJ'))

# ## Remove the founders, which I don't want to evaluate
# idx <- -(1:sum(n_founders))

res3 <- remlf90(y ~ sp,
  generic = list(
    E = list(incidence = Z[dat$sp != 'EJ', idx],
      covariance = S[idx, idx]),
    data = dat[dat$sp != 'EJ', ])
```

```
## Warning in remlf90(y ~ sp, generic = list(E = list(incidence = Z[dat$sp != : No specification of ini
## Using default value of 1 for all variance components.
## See ?breedR.getOption.
```



```
summary(res3)
```

```
## Linear Mixed Model with pedigree and spatial effects fit by AI-REMLF90 ver. 1.110
##   Data: dat[dat$sp != "EJ", ]
##   AIC  BIC logLik
## 5066 5076 -2531
##
## Variance components:
##           Estimated variances   S.E.
## E                3.391 0.8126
## Residual          1.013 0.3327
##
## Fixed effects:
##           value   s.e.
## sp.EE 0.21489 0.6171
## sp.EJ 0.00000 0.0000
## sp.JJ 0.15989 0.4981
```

Lambda was maximized at 0.65, giving an estimated additive-genetic variance for the J population of 2.2.

```
PBV <- as.matrix(Z[dat$sp != 'EJ', idx]) %*%
  do.call('rbind', lapply(ranef(res3), function(x) cbind(PBV = x, se = attr(x, 'se'))))

ggplot(cbind(dat[dat$sp != 'EJ', ], PBV), aes(bv, PBV)) +
  geom_point() +
  geom_abline(int = 0, sl = 1, col = 'darkgray')
```

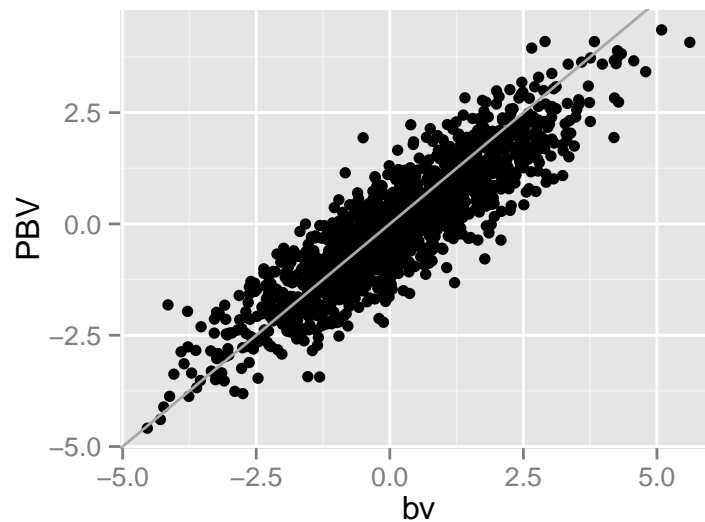


Figure 4: