**True Model:**

Spline:Degree=2, knots=c(7.6,14.3),

Speed : 5 covariates

Nonlinear mixed-effects model fit by maximum likelihood

Model: outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, beta3, beta4, ra1\_i, ra2\_i, ra3\_i, tau1 = 7.3, tau2 = 14.6, covar1 = var1, covar2 = var2, covar3 = var3, covar4 = var4, covar5 = var5, cov.coef1, cov.coef2, cov.coef3, cov.coef4, cov.coef5)

Data: sim.dt

AIC BIC logLik

20769.83 20873.04 -10367.92

Random effects:

Formula: list(ra1\_i ~ 1, ra2\_i ~ 1, ra3\_i ~ 1)

Level: id

Structure: General positive-definite, Log-Cholesky parametrization

StdDev Corr

ra1\_i 94.8752942 ra1\_i ra2\_i

ra2\_i 0.3189291 0.302

ra3\_i 0.3136059 0.298 0.300

Residual 1.0071790

Fixed effects: beta0 + beta1 + beta2 + beta3 + beta4 + cov.coef1 + cov.coef2 + cov.coef3 + cov.coef4 + cov.coef5 ~ 1

Value Std.Error DF t-value p-value

beta0 11.029669 4.707340 2791 2.34308 0.0192

beta1 4.900828 0.092987 2791 52.70431 0.0000

beta2 2.992511 0.023672 2791 126.41772 0.0000

beta3 0.695750 0.011265 2791 61.76236 0.0000

beta4 0.497350 0.003069 2791 162.03381 0.0000

cov.coef1 0.660725 0.043627 2791 15.14499 0.0000

cov.coef2 0.592704 0.046531 2791 12.73788 0.0000

cov.coef3 -0.387414 0.044267 2791 -8.75169 0.0000

cov.coef4 -1.265102 0.046007 2791 -27.49819 0.0000

cov.coef5 0.405671 0.027817 2791 14.58383 0.0000

Correlation:

beta0 beta1 beta2 beta3 beta4 cv.cf1 cv.cf2 cv.cf3 cv.cf4

beta1 -0.254

beta2 0.067 -0.112

beta3 0.045 0.171 0.762

beta4 0.132 -0.605 -0.194 -0.480

cov.coef1 0.043 -0.036 -0.029 -0.020 0.033

cov.coef2 0.038 -0.032 -0.026 -0.019 0.031 -0.271

cov.coef3 0.041 -0.038 -0.025 -0.026 0.028 -0.317 -0.219

cov.coef4 0.038 -0.039 -0.022 -0.030 0.022 -0.140 -0.387 -0.251

cov.coef5 0.026 -0.021 -0.018 -0.011 0.022 -0.159 -0.112 -0.175 -0.160

Standardized Within-Group Residuals:

Min Q1 Med Q3 Max

-2.796349380 -0.519043247 0.006889227 0.513706452 2.811878906

Number of Observations: 3200

Number of Groups: 400

>

> # compare with true fixed effect

> nlme\_d2k2$coefficients$fixed

beta0 beta1 beta2 beta3 beta4 cov.coef1 cov.coef2 cov.coef3 cov.coef4 cov.coef5

11.0296685 4.9008285 2.9925112 0.6957497 0.4973496 0.6607245 0.5927038 -0.3874135 -1.2651017 0.4056712

> sp.coeff1

[1] 10.0 5.0 3.0 0.7 0.5

> cov.coeff1

[1] 0.7 0.5 -0.4 -1.2 0.4

**Decrease ra\_1（intercept on y）**

Error in solve.default(pdMatrix(a, factor = TRUE)) :

system is computationally singular: reciprocal condition number = 2.19849e-80

**Inrease error term:** rnorm(n=length(time),mean=0,sd=1)\*100

Error in solve.default(pdMatrix(a, factor = TRUE)) :

system is computationally singular: reciprocal condition number = 1.94522e-31

In addition: Warning messages:

1: In nlme.formula(outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, :

Iteration 1, LME step: nlminb() did not converge (code = 1). Do increase 'msMaxIter'!

2: In nlme.formula(outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, :

Singular precision matrix in level -1, block 1

**Bad starting value: (identical result as true model)**

start.true =c(beta0 = 1, beta1 =1,beta2 = 1,beta3 = 1,beta4 = 1,

cov.coef1 = 1,cov.coef2 = 1, cov.coef3 = -1,cov.coef4 = -1,cov.coef5 = 1)

|  |
| --- |
| Nonlinear mixed-effects model fit by maximum likelihood  Model: outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, beta3, beta4, ra1\_i, ra2\_i, ra3\_i, tau1 = 7.3, tau2 = 14.6, covar1 = var1, covar2 = var2, covar3 = var3, covar4 = var4, covar5 = var5, cov.coef1, cov.coef2, cov.coef3, cov.coef4, cov.coef5)  Data: sim.dt  AIC BIC logLik  20769.84 20873.05 -10367.92  Random effects:  Formula: list(ra1\_i ~ 1, ra2\_i ~ 1, ra3\_i ~ 1)  Level: id  Structure: General positive-definite, Log-Cholesky parametrization  StdDev Corr  ra1\_i 94.8754219 ra1\_i ra2\_i  ra2\_i 0.3189287 0.302  ra3\_i 0.3136049 0.298 0.300  Residual 1.0071780  Fixed effects: beta0 + beta1 + beta2 + beta3 + beta4 + cov.coef1 + cov.coef2 + cov.coef3 + cov.coef4 + cov.coef5 ~ 1  Value Std.Error DF t-value p-value  beta0 11.038735 4.707364 2791 2.34499 0.0191  beta1 4.900260 0.092991 2791 52.69614 0.0000  beta2 2.992559 0.023672 2791 126.41553 0.0000  beta3 0.695772 0.011265 2791 61.76214 0.0000  beta4 0.497363 0.003070 2791 162.03051 0.0000  cov.coef1 0.660726 0.043627 2791 15.14497 0.0000  cov.coef2 0.592790 0.046530 2791 12.73989 0.0000  cov.coef3 -0.387345 0.044267 2791 -8.75023 0.0000  cov.coef4 -1.265213 0.046006 2791 -27.50097 0.0000  cov.coef5 0.405716 0.027816 2791 14.58548 0.0000  Correlation:  beta0 beta1 beta2 beta3 beta4 cv.cf1 cv.cf2 cv.cf3 cv.cf4  beta1 -0.254  beta2 0.067 -0.112  beta3 0.045 0.171 0.762  beta4 0.132 -0.605 -0.193 -0.480  cov.coef1 0.043 -0.036 -0.029 -0.020 0.033  cov.coef2 0.038 -0.032 -0.026 -0.019 0.031 -0.271  cov.coef3 0.041 -0.038 -0.025 -0.026 0.028 -0.317 -0.219  cov.coef4 0.038 -0.039 -0.022 -0.030 0.022 -0.140 -0.387 -0.251  cov.coef5 0.026 -0.021 -0.018 -0.011 0.022 -0.159 -0.112 -0.175 -0.160  Standardized Within-Group Residuals:  Min Q1 Med Q3 Max  -2.796329885 -0.519021420 0.006525355 0.513692700 2.811887007  Number of Observations: 3200  Number of Groups: 400  >  > # compare with true fixed effect  > nlme\_d2k2$coefficients$fixed  beta0 beta1 beta2 beta3 beta4 cov.coef1 cov.coef2 cov.coef3 cov.coef4 cov.coef5  11.0387353 4.9002600 2.9925586 0.6957719 0.4973627 0.6607263 0.5927898 -0.3873447 -1.2652127 0.4057162  > sp.coeff1  [1] 10.0 5.0 3.0 0.7 0.5  > cov.coeff1  [1] 0.7 0.5 -0.4 -1.2 0.4 |
|  |
| |  | | --- | |  | |

**No covariates**

Warning message:

In nlme.formula(outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, :

Iteration 1, LME step: nlminb() did not converge (code = 1). Do increase 'msMaxIter'!

>

> summary(nlme\_d2k2)

Nonlinear mixed-effects model fit by maximum likelihood

Model: outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, beta3, beta4, ra1\_i, ra2\_i, ra3\_i, tau1 = 7.3, tau2 = 14.6)

Data: sim.dt

AIC BIC logLik

21307.61 21380.46 -10641.81

Random effects:

Formula: list(ra1\_i ~ 1, ra2\_i ~ 1, ra3\_i ~ 1)

Level: id

Structure: General positive-definite, Log-Cholesky parametrization

StdDev Corr

ra1\_i 94.8719937 ra1\_i ra2\_i

ra2\_i 0.3187584 0.302

ra3\_i 0.5918592 0.185 0.167

Residual 1.0073076

Fixed effects: beta0 + beta1 + beta2 + beta3 + beta4 ~ 1

Value Std.Error DF t-value p-value

beta0 10.119654 4.647735 2796 2.17733 0.0295

beta1 4.914999 0.092285 2796 53.25895 0.0000

beta2 2.995476 0.023645 2796 126.68751 0.0000

beta3 0.696880 0.011241 2796 61.99500 0.0000

beta4 0.496940 0.003056 2796 162.63117 0.0000

Correlation:

beta0 beta1 beta2 beta3

beta1 -0.241

beta2 0.080 -0.121

beta3 0.056 0.164 0.762

beta4 0.120 -0.601 -0.189 -0.478

Standardized Within-Group Residuals:

Min Q1 Med Q3 Max

-2.793795007 -0.518870688 0.005405808 0.512692090 2.812826879

Number of Observations: 3200

Number of Groups: 400

>

> # compare with true fixed effect

> nlme\_d2k2$coefficients$fixed

beta0 beta1 beta2 beta3 beta4

10.1196542 4.9149990 2.9954758 0.6968798 0.4969400

> sp.coeff1

[1] 10.0 5.0 3.0 0.7 0.5

> cov.coeff1

[1] 0.7 0.5 -0.4 -1.2 0.4

**Wrong knots:**

Knots=c(10,17)

Warning message:

In nlme.formula(outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, :

Iteration 8, LME step: nlminb() did not converge (code = 1). PORT message: false convergence (8)

>

> summary(nlme\_d2k2)

Nonlinear mixed-effects model fit by maximum likelihood

Model: outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, beta3, beta4, ra1\_i, ra2\_i, ra3\_i, tau1 = 10, tau2 = 17, covar1 = var1, covar2 = var2, covar3 = var3, covar4 = var4, covar5 = var5, cov.coef1, cov.coef2, cov.coef3, cov.coef4, cov.coef5)

Data: sim.dt

AIC BIC logLik

21322.62 21425.82 -10644.31

Random effects:

Formula: list(ra1\_i ~ 1, ra2\_i ~ 1, ra3\_i ~ 1)

Level: id

Structure: General positive-definite, Log-Cholesky parametrization

StdDev Corr

ra1\_i 94.9270756 ra1\_i ra2\_i

ra2\_i 0.3727195 0.307

ra3\_i 0.3173497 0.303 0.327

Residual 1.1497887

Fixed effects: beta0 + beta1 + beta2 + beta3 + beta4 + cov.coef1 + cov.coef2 + cov.coef3 + cov.coef4 + cov.coef5 ~ 1

Value Std.Error DF t-value p-value

beta0 13.817343 4.717112 2791 2.92920 0.0034

beta1 3.262775 0.085986 2791 37.94522 0.0000

beta2 2.299195 0.028224 2791 81.46153 0.0000

beta3 0.460815 0.012428 2791 37.08010 0.0000

beta4 0.321634 0.004029 2791 79.82751 0.0000

cov.coef1 0.726753 0.043828 2791 16.58191 0.0000

cov.coef2 0.654909 0.046733 2791 14.01391 0.0000

cov.coef3 -0.316112 0.044464 2791 -7.10938 0.0000

cov.coef4 -1.191284 0.046213 2791 -25.77813 0.0000

cov.coef5 0.430109 0.027924 2791 15.40290 0.0000

Correlation:

beta0 beta1 beta2 beta3 beta4 cv.cf1 cv.cf2 cv.cf3 cv.cf4

beta1 -0.269

beta2 0.058 -0.060

beta3 0.029 0.153 0.897

beta4 0.067 -0.422 -0.685 -0.847

cov.coef1 0.044 -0.043 -0.051 -0.047 0.056

cov.coef2 0.038 -0.038 -0.046 -0.042 0.050 -0.269

cov.coef3 0.042 -0.043 -0.048 -0.050 0.051 -0.314 -0.217

cov.coef4 0.039 -0.043 -0.044 -0.052 0.046 -0.137 -0.385 -0.248

cov.coef5 0.027 -0.025 -0.031 -0.027 0.034 -0.157 -0.110 -0.174 -0.159

Standardized Within-Group Residuals:

Min Q1 Med Q3 Max

-2.63198348 -0.50670370 0.01832341 0.52065307 2.88538942

Number of Observations: 3200

Number of Groups: 400

>

> # compare with true fixed effect

> nlme\_d2k2$coefficients$fixed

beta0 beta1 beta2 beta3 beta4 cov.coef1 cov.coef2 cov.coef3 cov.coef4 cov.coef5

13.8173428 3.2627752 2.2991948 0.4608148 0.3216337 0.7267530 0.6549088 -0.3161116 -1.1912839 0.4301091

> sp.coeff1

[1] 10.0 5.0 3.0 0.7 0.5

> cov.coeff1

[1] 0.7 0.5 -0.4 -1.2 0.4

**Fit with one knot: tau1=7.3**

Nonlinear mixed-effects model fit by maximum likelihood

Model: outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, beta3, ra1\_i, ra2\_i, ra3\_i, tau1 = 7.3, covar1 = var1, covar2 = var2, covar3 = var3, covar4 = var4, covar5 = var5, cov.coef1, cov.coef2, cov.coef3, cov.coef4, cov.coef5)

Data: sim.dt

AIC BIC logLik

23414.76 23511.9 -11691.38

Random effects:

Formula: list(ra1\_i ~ 1, ra2\_i ~ 1, ra3\_i ~ 1)

Level: id

Structure: General positive-definite, Log-Cholesky parametrization

StdDev Corr

ra1\_i 95.0765171 ra1\_i ra2\_i

ra2\_i 0.1983334 0.321

ra3\_i 0.3458388 0.269 0.404

Residual 1.8877600

Fixed effects: beta0 + beta1 + beta2 + beta3 + cov.coef1 + cov.coef2 + cov.coef3 + cov.coef4 + cov.coef5 ~ 1

Value Std.Error DF t-value p-value

beta0 17.266846 4.737315 2792 3.64486 3e-04

beta1 4.010298 0.187834 2792 21.35022 0e+00

beta2 8.908317 0.069117 2792 128.88685 0e+00

beta3 2.362472 0.014741 2792 160.26412 0e+00

cov.coef1 0.416442 0.046932 2792 8.87326 0e+00

cov.coef2 0.370739 0.050038 2792 7.40910 0e+00

cov.coef3 -0.581301 0.047582 2792 -12.21696 0e+00

cov.coef4 -1.421861 0.049515 2792 -28.71582 0e+00

cov.coef5 0.304711 0.029920 2792 10.18426 0e+00

Correlation:

beta0 beta1 beta2 beta3 cv.cf1 cv.cf2 cv.cf3 cv.cf4

beta1 -0.292

beta2 0.124 -0.561

beta3 0.128 -0.316 0.512

cov.coef1 0.038 -0.040 -0.016 0.030

cov.coef2 0.034 -0.035 -0.012 0.028 -0.269

cov.coef3 0.037 -0.039 -0.006 -0.003 -0.317 -0.219

cov.coef4 0.034 -0.040 0.005 -0.033 -0.141 -0.388 -0.249

cov.coef5 0.023 -0.024 -0.011 0.028 -0.157 -0.110 -0.176 -0.161

Standardized Within-Group Residuals:

Min Q1 Med Q3 Max

-2.553871297 -0.526487308 0.004616529 0.549025623 2.639967325

Number of Observations: 3200

Number of Groups: 400

>

> # compare with true fixed effect

> nlme\_d2k2$coefficients$fixed

beta0 beta1 beta2 beta3 cov.coef1 cov.coef2 cov.coef3 cov.coef4 cov.coef5

17.2668460 4.0102983 8.9083165 2.3624716 0.4164421 0.3707386 -0.5813012 -1.4218608 0.3047110

> sp.coeff1

[1] 10.0 5.0 3.0 0.7 0.5

> cov.coeff1

[1] 0.7 0.5 -0.4 -1.2 0.4

**Add a cubic term:**

Warning message:

In nlme.formula(outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, :

Iteration 18, LME step: nlminb() did not converge (code = 1). PORT message: false convergence (8)

>

> summary(nlme\_d2k2)

Nonlinear mixed-effects model fit by maximum likelihood

Model: outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, beta3, beta4, beta5, ra1\_i, ra2\_i, ra3\_i, tau1 = 7.3, tau2 = 14.6, covar1 = var1, covar2 = var2, covar3 = var3, covar4 = var4, covar5 = var5, cov.coef1, cov.coef2, cov.coef3, cov.coef4, cov.coef5)

Data: sim.dt

AIC BIC logLik

20771.81 20881.09 -10367.91

Random effects:

Formula: list(ra1\_i ~ 1, ra2\_i ~ 1, ra3\_i ~ 1)

Level: id

Structure: General positive-definite, Log-Cholesky parametrization

StdDev Corr

ra1\_i 94.8755323 ra1\_i ra2\_i

ra2\_i 0.3189365 0.302

ra3\_i 0.3136049 0.298 0.300

Residual 1.0071711

Fixed effects: beta0 + beta1 + beta2 + beta3 + beta4 + beta5 + cov.coef1 + cov.coef2 + cov.coef3 + cov.coef4 + cov.coef5 ~ 1

Value Std.Error DF t-value p-value

beta0 11.012413 4.708189 2790 2.33899 0.0194

beta1 4.902057 0.093000 2790 52.71027 0.0000

beta2 2.992176 0.025286 2790 118.33314 0.0000

beta3 0.695647 0.011490 2790 60.54166 0.0000

beta4 0.497291 0.003238 2790 153.59666 0.0000

beta5 0.000000 0.000010 2790 0.03056 0.9756

cov.coef1 0.660753 0.043638 2790 15.14171 0.0000

cov.coef2 0.592827 0.046542 2790 12.73755 0.0000

cov.coef3 -0.387431 0.044277 2790 -8.75013 0.0000

cov.coef4 -1.265261 0.046017 2790 -27.49556 0.0000

cov.coef5 0.405720 0.027822 2790 14.58266 0.0000

Correlation:

beta0 beta1 beta2 beta3 beta4 beta5 cv.cf1 cv.cf2 cv.cf3 cv.cf4

beta1 -0.254

beta2 0.065 -0.110

beta3 0.046 0.165 0.769

beta4 0.128 -0.579 -0.060 -0.384

beta5 -0.007 0.015 -0.351 -0.196 -0.317

cov.coef1 0.043 -0.036 -0.032 -0.022 0.027 0.014

cov.coef2 0.038 -0.032 -0.029 -0.021 0.025 0.012 -0.271

cov.coef3 0.041 -0.037 -0.028 -0.027 0.023 0.011 -0.317 -0.219

cov.coef4 0.038 -0.038 -0.024 -0.031 0.017 0.010 -0.139 -0.387 -0.251

cov.coef5 0.026 -0.021 -0.020 -0.012 0.018 0.008 -0.159 -0.111 -0.175 -0.160

Standardized Within-Group Residuals:

Min Q1 Med Q3 Max

-2.795730607 -0.519131463 0.007065908 0.513624161 2.811919424

Number of Observations: 3200

Number of Groups: 400

>

> # compare with true fixed effect

> nlme\_d2k2$coefficients$fixed

beta0 beta1 beta2 beta3 beta4 beta5 cov.coef1 cov.coef2

1.101241e+01 4.902057e+00 2.992176e+00 6.956467e-01 4.972907e-01 3.052855e-07 6.607531e-01 5.928271e-01

cov.coef3 cov.coef4 cov.coef5

-3.874315e-01 -1.265261e+00 4.057196e-01

> sp.coeff1

[1] 10.0 5.0 3.0 0.7 0.5

> cov.coeff1

[1] 0.7 0.5 -0.4 -1.2 0.4

**Add one extra knot:**

Nonlinear mixed-effects model fit by maximum likelihood

Model: outcome ~ d2k2\_model(time = age, beta0, beta1, beta2, beta3, beta4, beta5, ra1\_i, ra2\_i, ra3\_i, tau1 = 7.3, tau2 = 14.6, tau3 = 18, covar1 = var1, covar2 = var2, covar3 = var3, covar4 = var4, covar5 = var5, cov.coef1, cov.coef2, cov.coef3, cov.coef4, cov.coef5)

Data: sim.dt

AIC BIC logLik

20775.4 20884.68 -10369.7

Random effects:

Formula: list(ra1\_i ~ 1, ra2\_i ~ 1, ra3\_i ~ 1)

Level: id

Structure: General positive-definite, Log-Cholesky parametrization

StdDev Corr

ra1\_i 94.8775660 ra1\_i ra2\_i

ra2\_i 0.3173546 0.302

ra3\_i 0.3136399 0.298 0.301

Residual 1.0079951

Fixed effects: beta0 + beta1 + beta2 + beta3 + beta4 + beta5 + cov.coef1 + cov.coef2 + cov.coef3 + cov.coef4 + cov.coef5 ~ 1

Value Std.Error DF t-value p-value

beta0 11.194614 4.712180 2790 2.37568 0.0176

beta1 4.894499 0.093783 2790 52.18976 0.0000

beta2 3.025788 0.047669 2790 63.47474 0.0000

beta3 0.702642 0.014224 2790 49.39904 0.0000

beta4 0.507142 0.012499 2790 40.57445 0.0000

beta5 -0.008385 0.010417 2790 -0.80490 0.4209

cov.coef1 0.658696 0.043710 2790 15.06979 0.0000

cov.coef2 0.590839 0.046598 2790 12.67944 0.0000

cov.coef3 -0.389308 0.044332 2790 -8.78170 0.0000

cov.coef4 -1.266939 0.046062 2790 -27.50537 0.0000

cov.coef5 0.404829 0.027837 2790 14.54302 0.0000

Correlation:

beta0 beta1 beta2 beta3 beta4 beta5 cv.cf1 cv.cf2 cv.cf3 cv.cf4

beta1 -0.257

beta2 0.069 -0.124

beta3 0.060 0.085 0.828

beta4 0.072 -0.225 0.812 0.488

beta5 -0.041 0.079 -0.865 -0.604 -0.969

cov.coef1 0.040 -0.031 -0.067 -0.052 -0.050 0.060

cov.coef2 0.036 -0.028 -0.058 -0.047 -0.043 0.052 -0.267

cov.coef3 0.039 -0.033 -0.058 -0.052 -0.044 0.052 -0.313 -0.216

cov.coef4 0.036 -0.035 -0.052 -0.052 -0.040 0.047 -0.136 -0.384 -0.248

cov.coef5 0.025 -0.018 -0.040 -0.030 -0.029 0.036 -0.157 -0.109 -0.173 -0.158

Standardized Within-Group Residuals:

Min Q1 Med Q3 Max

-2.799625689 -0.515859716 0.007697877 0.515079532 2.791740821

Number of Observations: 3200

Number of Groups: 400

>

> # compare with true fixed effect

> nlme\_d2k2$coefficients$fixed

beta0 beta1 beta2 beta3 beta4 beta5 cov.coef1 cov.coef2 cov.coef3

11.194614240 4.894499342 3.025787591 0.702642120 0.507141577 -0.008384859 0.658696171 0.590839202 -0.389307878

cov.coef4 cov.coef5

-1.266939190 0.404829247

> sp.coeff1

[1] 10.0 5.0 3.0 0.7 0.5

> cov.coeff1

[1] 0.7 0.5 -0.4 -1.2 0.4