

Onychomycosis Report

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1 Introduction

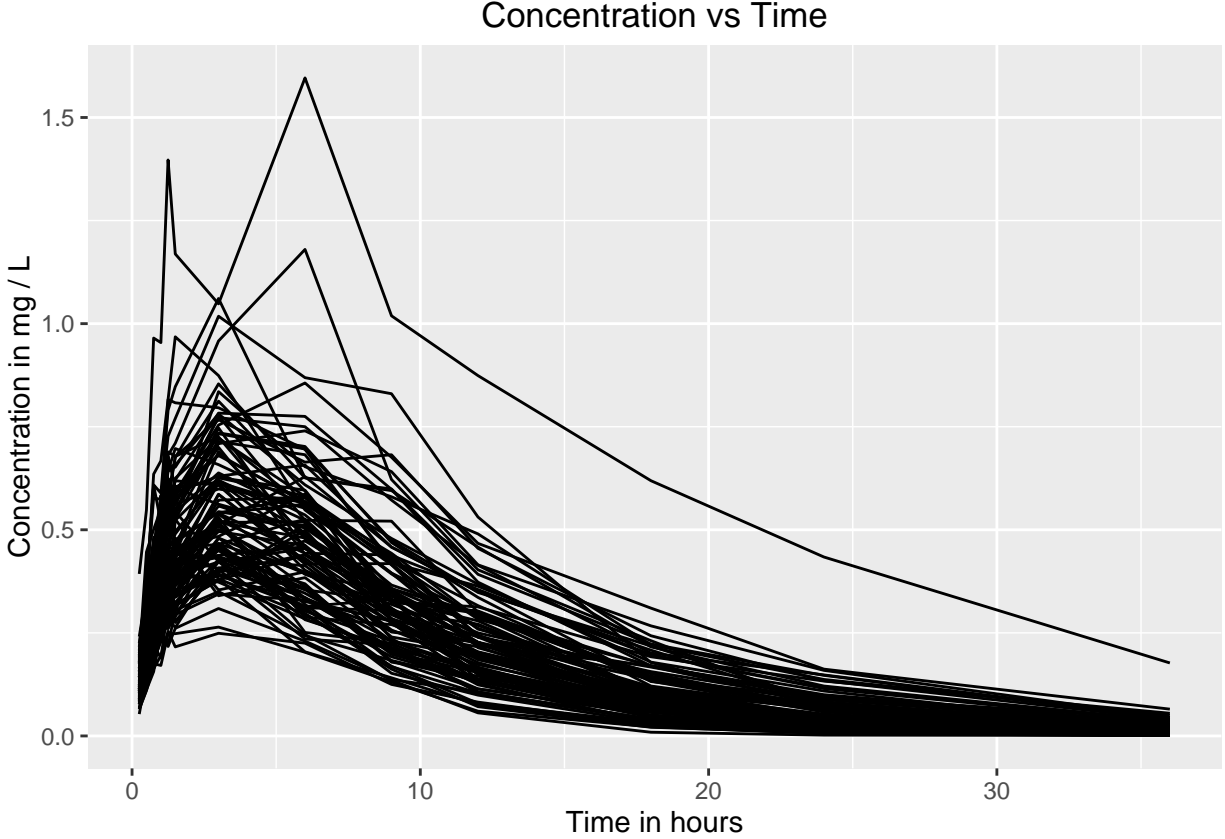
This document will provide an provide an analysis of the Onychomycosis data. The data came from 3 studies: a pharmacokinetic study, a longitudinal study of nail growth, and a pilot comparative longitudinal study of disease severity. Each dataset was fit to multiple longitudinal models, and the models were used to answer the research questions of each study. These models are more sophisticated than typical linear models, and allow us to take advantage of the structure of the data, namely that each subject was measured at multiple time points in the studies. It is reasonable to expect that measurements made on the same subject, and measurements made at nearby times within a subject may be correlated, which violates our typical linear model assumptions, but can be handled by longitudinal models. This approach also allow for the model parameters to be distinct for each patient, by incorporating them as random effects - quantities which vary randomly in the population and may be affected by patient characteristics, such as weight, gender, or age. The data may not be well described by a linear combination (or function of a linear combination) of the covariates, giving rise to the need for nonlinear models.

2 Analyses

Pharmacokinetic Study

The data provided consist of repeated measurements of diptroconazole concentrations evaluated at 13 times over a 36 hour period on each of 100 patients, in addition to information about patient characteristics including weight, age, gender, and creatinine clearance. The goal of the analysis is to determine if there is any association between a patients pharmacokinetic parameters (absorption, distribution, elimination) and their aforementioned characteristics. The research questions suggests a subject specific approach, which was used in the modeling process.

A one-compartment model for the mean of drug concentration may be useful to answer the research questions, as this type of model is defined by absorption, distribution, and elimination parameters. An visual examination of the data confirms that the trend of the data resembles a one-compartment model.



A one-compartment nonlinear mixed effects model was used to fit the data. This approach allows us to account for the nonlinearity in the data and to answer subject specific questions. We initially consider 2 models, the first model includes none of the covariates, and models each of the pharmacokinetic parameters as an exponential function of a normal random variable, or equivalently we are modeling in terms of the logarithms of our pharmacokinetic parameters. The normal random variables, $\beta_i = (\beta_{kai}, \beta_{Cli}, \beta_{Vi}) \sim N(E(\beta_i), D)$, where in this example β_i is simply a vector of intercept terms (they don't change with the covariates). The second model representation introduces dependence of the mean of β_i on all of the characteristics. As a concrete example, we are representing $\log(ka_i) = \beta_{kai} = \beta_{ka0} + \beta_{kaA}Age + \beta_{kaW}Weight + \beta_{kaG}Gender + \beta_{kaC}CreatinineClearance + b_{kai}$, $b_{kai} \sim n(0, D_{1,1})$.

We fit the models using the R function nlme, which allows us to do nonlinear mixed effects modeling of our data. After obtaining starting values for the parameters, the parameters are estimated using maximum likelihood estimation. When we run this full model we find that most of the β terms are not significant (p-values greater than 0.05), except between weight, and both of β_{Cli}, β_{Vi} . This suggests a new model, which we will call the weight model, where β_{kai} is treated as having an intercept only, and β_{Cli}, β_{Vi} are modeled as linear functions of weight.

A comparison of the 3 models suggests that the weight model is the best fit to the data in terms of both AIC and BIC, 2 common metrics used for comparing nested models. The research question for this study asks if patient characteristics are associated with pharmacokinetic parameters and can be rephrased in the following form: which of these β coefficients are statistically significant? We chose the weight model, which contains all significant terms, so we can conclude that Clearance and Volume are significantly associated with weight. Model comparisons, parameter estimates, and standard errors are all reported in the appendix.

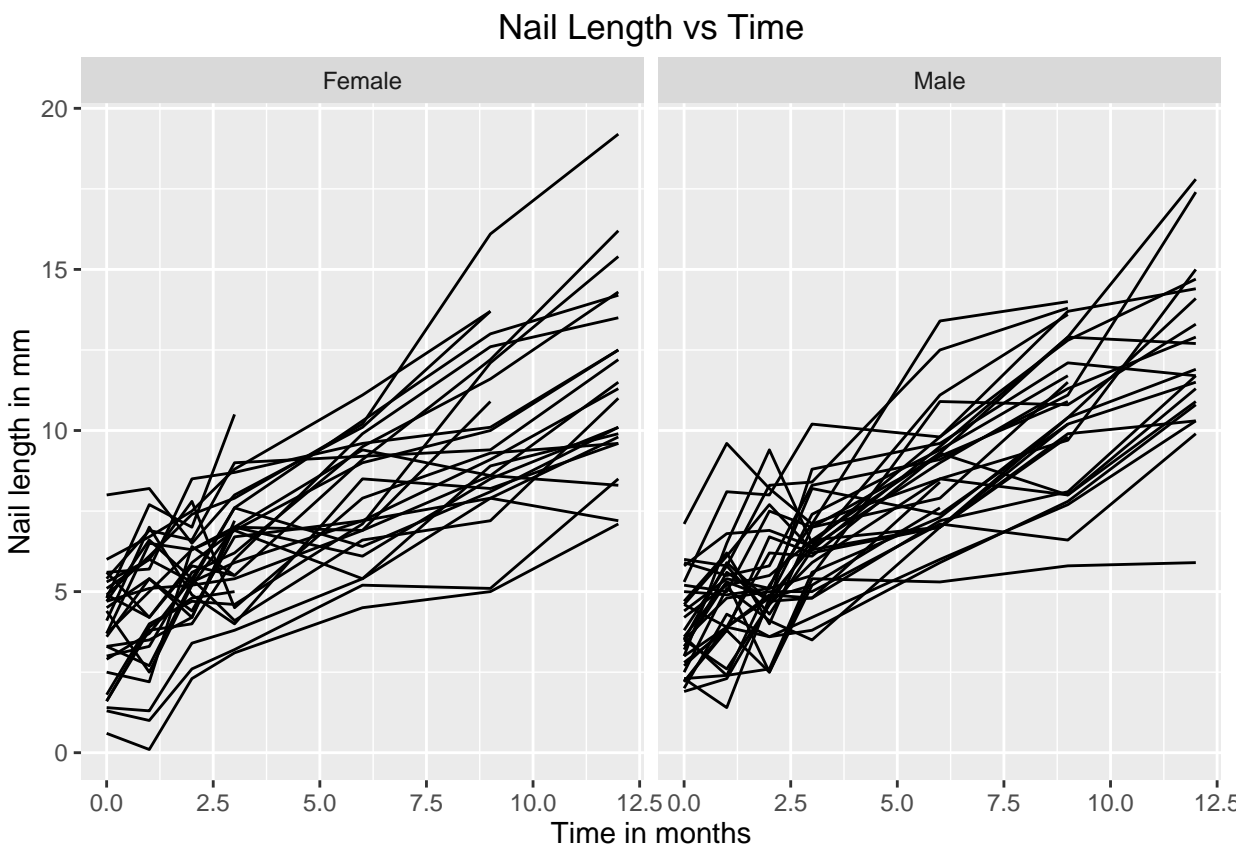
The correctness of the analysis relies on having the correct model for the mean, and power law coefficient of variation relationship. The one-compartment model is a consequence of the physics of pharmacokinetics, and the shape of the data appear to support the claim that this is a reasonable model. The research question is of scientific importance because it is important to know that weight has an impact on pharmacokinetic

parameters and allows us to create an approximation for clearance to be used in the longitudinal study of nail growth.

Longitudinal Study of Nail Growth

The data provide repeated measurements of unaffected nail length following the removal of a the afflicted part of a toenail and beginning a diptroconazole treatment. The data were intended to be recorded at 7 times during the study along with baseline characteristics such as gender, weight, and age. However, some of the data were missing, which impacts the analysis. The goal of the study was to see if and how unaffected nail length increased over time. The research questions suggest a subject specific approach.

An initial examination of the data suggests that unaffected nail length increases over time. Furthermore the nail lengths for each gender seem to be roughly linearly increasing with time.



A linear mixed effects model was used to model the data. This model assumes that nail length is a linear function of time and other characteristics, but that individuals in the population may have their own unique slope and intercept. Since the model used is linear, the parameter estimates will be the same as they would have been if we took a population average approach. This model was chosen for its flexibility in allowing a unique slope and intercept for each patient, in addition to allowing us to incorporate a correlation structure that models the correlation of measurements taken at different time points.

We start with a model that has no variables other than time from there we build to models which have just gender terms for the slope and intercept, and then we add gender into the model (it seems likely from the spaghetti plots that values are separate for males vs females). We then construct a model with age and gender.

Using the results of the pharmacokinetic study, we can create a variable to crudely measure the availability of a metabolite by using an approximation to clearance. The pharmacokinetic study found a significant linear

relationship between the log of clearance and weight. Recalling that this log-clearance variable was modeled as a random normal quantity, we use the typical value for the quantity, which corresponds to the following relationship $\log(Clearance) \approx 2.436994 + 0.013294Weight$. We take an exponential function of this quantity and can use this as a proxy for metabolite availability.

The research question only asks if this quantity is related to the slope, so we incorporate this into the slope of the model and see that the resultant p-value for this term is barely above 0.05. In light of this, and the fact that age was not significant in the model, we consider a model with only gender and this surrogate for metabolite.

We fit the models using the R function `lme`, which allows us to do linear mixed effects modeling of our data. The missing data seems to be due to dropout, but we took precautions since we did not know whether there are systematic biases to the pattern of missingness in the data. To account for this, the parameters are estimated using maximum likelihood estimation. A comparison of all of the models (13 in total) suggests that the model using only gender is the best fit to the data in terms of both AIC and BIC.

The research questions about the variables can be posed as questions about the coefficients of the corresponding variables in our model. To decide if unaffected nail length before treatment is associated with age or gender we examine the significance of the intercept terms for age and gender. Age is not significant in any model, and gender is significant in almost every model, so there is a relationship with gender, but not age. Similarly, the rate of growth of nail length is associated with gender, but not age, which can be discerned by looking at the significance of the linear (slope) terms for age and gender. We cannot conclusively say that our metabolite approximation is related to nail length rate of growth (slope), because in all of the models that include it, the corresponding p-values are between 0.05 and 0.08. However, given that we only used an approximation we believe the relationship between metabolite availability and unaffected nail length may warrant additional study. The nature of the pattern of change is linear, as evidenced by the significance of the slope terms.

Ultimately we selected the model with common (shared for both genders) diagonal within-subject (over time) covariance matrix that contained only gender and time as covariates. Model comparisons, parameter estimates, and standard errors are all reported in the appendix. The correctness of this model depends on whether the random effects were normal, measurement error variance was stationary, and if we correctly specified the mean and random effect covariance functions. These seem like reasonable assumptions given a visual inspection of the data.

Pilot Comparative Longitudinal Study of Disease Severity

The data for this study come from a randomized clinical trial of 200 onychomycosis sufferers. Patients were administered dipiroconazole and itraconazole at baseline and had the severity of their infection rated at baseline and 3 other times over the following 6 months. Also collected were baseline patient characteristics including age and gender.

Since the response variable (severity) consists of 1's and 0's, a spaghetti plot may be uninformative. However, we can count the proportion that have severe infection at each time point and group by which treatment the patient recieved (even if there is a baseline difference, the treatment is not causing a difference at time 0).

```
## severity.0 severity.1 severity.3 severity.6
## 0.3663366 0.3564356 0.3168317 0.1782178
```

```
## severity.0 severity.1 severity.3 severity.6
## 0.4141414 0.3737374 0.2121212 0.1010101
```

The proportion who have severe infection seems to be decreasing over time for both treatments, and to a greater extent for dipiroconazole. The response variable is binary, so it seems natural to model the probability of having a severe infection given covariates. We use the logistic function applied to a linear combination of the covariates, which ensures that our fitted values for severity will fall between 0 and 1. This is the

mechanism used in logistic regression, except that we have 4 (likely correlated) responses on each individual, and we will need to model this correlation structure in addition to the coefficient parameters for the covariates. We took a population average perspective in modeling this data. This model was chosen for its ability to model binary data and incorporate a correlation structure between observations made on the same individual.

We initially consider a model with no covariates and an unstructured correlation matrix (the correlation is between time points for an individual), because we have balanced data and enough of it to estimate this rich structure. We then model the expected log-odds of a severe nail infection as linear function of age, gender, time, and the product of treatment and time. The intuition is that age and gender may be related to probability of a severe nail infection at baseline, this probability may change over time, and the change over time may be different depending on the treatment administered.

We run this full model with 3 correlation structures: independence, compound symmetry, and unstructured. Loosely speaking, independence means there is no dependence between any of the measurements of nail severity within an individual, compound symmetry means there is constant correlation between any two measurements, and unstructured means that each correlation is allowed to take a unique value (maximum flexibility). All 3 models show a consistent trend in which variables are significant. We use the robust standard errors and find that the time variable and the time-by-treatment variable are the only significant terms, no matter which model we used. The estimated unstructured correlation matrix suggests that the correlation tapers off over time, so is not consistent with independence or compound symmetric models.

We use this information to fit a reduced model with only the time and the time-by-treatment variables, again using all 3 correlation structures. Similarly, the unstructured correlation suggests that the correlation between responses tapers slightly over time, so independence and compound symmetry do not appear reasonable. We settle on the reduced model with unstructured correlation as our final model for the data.

The research questions about the variables can be posed as questions about the coefficients of the corresponding variables in our model. There was not evidence to conclude the percentage of onychomycosis sufferers having severe infection prior to treatment was different based on age or gender, evidenced by the fact that the coefficients for age and gender were not significant. There is evidence to suggest that the odds of severe infection decrease over time for both groups, which is equivalent to test $H_0 : \beta_{time} > 0$ vs $H_A : \beta_{time} < 0$, which we reject at the 0.05 level of significance. Similarly, there is evidence to suggest that the odds of severe infection decrease more quickly for treatment = 1 (diptroconazole) group, which is equivalent to testing $H_0 : \beta_{time,treatment} > 0$ vs $H_A : \beta_{time,treatment} < 0$, which we also reject at the 0.05 level of significance.

We fit the models using the R function `gee`, which allows us to estimate a nonlinear population average model using generalized estimating equations. Direct model comparisons are difficult in this setting, so we chose the model based on flexibility and statistical significance of the predictors, as measured by the robust standard errors. Parameter estimates, and standard errors are all reported in the appendix. The correctness of this model depends on whether the use of the logistic function was correct, measurement error variance was constant, and the unstructured correlation matrix was correct.

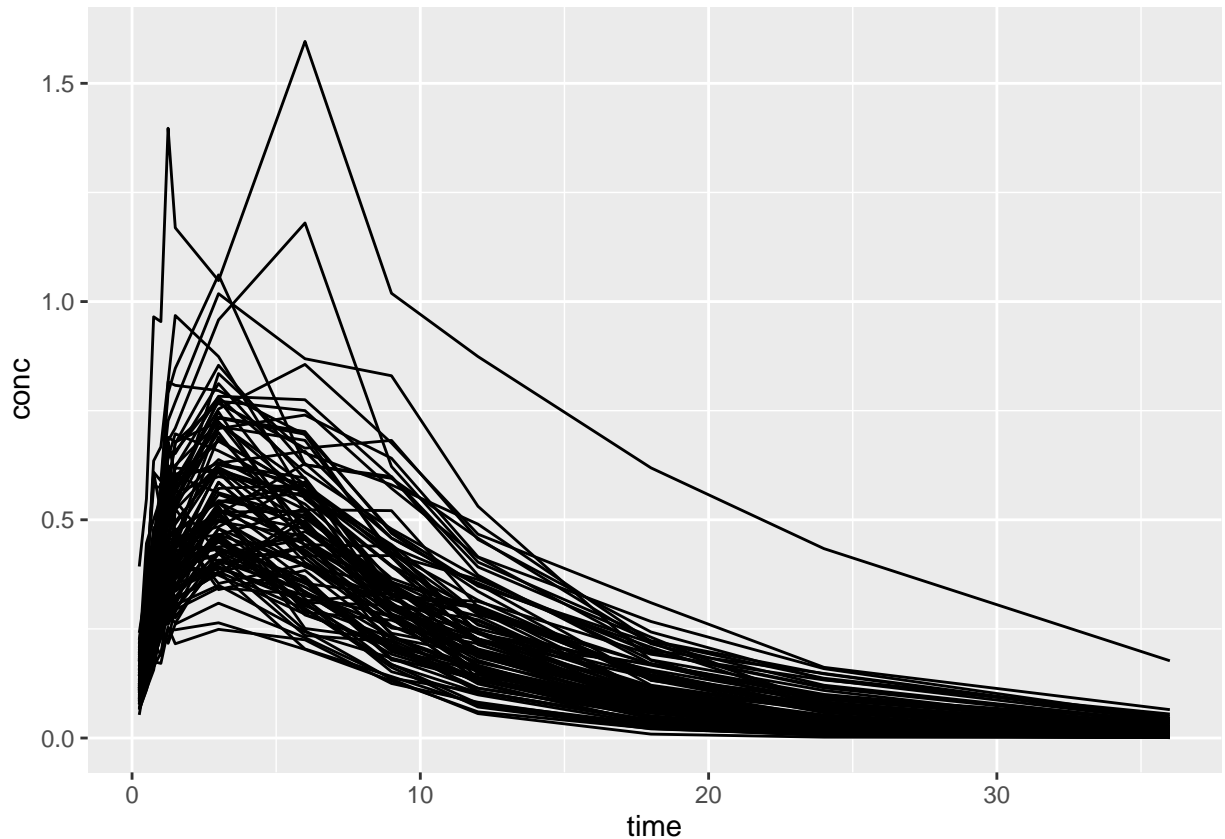
3 Conclusions

The analyses of these 3 studies suggest that diptroconazole has great promise in treating symptoms of onychomycosis. Assuming that our models are correct, we can reach a few conclusions. The pharmacokinetic properties of diptroconazole depend on the weight of the patient, so dosing strategies must be tailored based on patient weight. Furthermore, after beginning treatment on diptroconazole, the length of the unaffected portion of a nail increases linearly over time, and the rate of change is different for males and females. Metabolite availability may or may not be related to the rate of change of nail length, and this warrants further study. Finally, we were able to conclude that patients taking diptroconazole instead of intraconazole had a faster decrease in the odds of a having a severe nail infection over the first 6 months taking the drug. In this way, diptroconazole outperforms the existing solution for treatment of onychomycosis.

4 Appendix

The appendix contains all of the code used to generate the models and conclusions in this report.

```
####  
#### Pharmacokinetic study  
####  
  
library(nlme)  
  
## define the one compartment model function for individual mean  
  
meanfunc <- function(t,K_star,C_star,V_star){  
  
  K = exp(K_star)  
  C = exp(C_star)  
  V = exp(V_star)  
  D = 200  
  
  fpl_A = K * D / (V * (K - C / V))  
  fpl_B = exp(-C * t / V) - exp(-K * t)  
  fpl = fpl_A * fpl_B  
  
  ##Derivatives were calculated, but caused nlme to fail, so I didn't use them  
  
  meangrad <- array(0,c(length(t),3),list(NULL,c("b1","b2","b3")))  
  meangrad[,"b1"] <- D / V * (K * C / V)/(K - C / V)^2 * fpl_B + fpl_A * (-exp(-K * t) * (-K * t))  
  meangrad[,"b2"] <- K * D / V * (C / V) / (K - C / V)^2 * fpl_B + fpl_A * (exp(- C * t / V) * (-K * t))  
  meangrad[,"b3"] <- K * D * (-V * K) / (V * K - C)^2 * fpl_B + fpl_A * (exp(- C * t / V) * (-K * t) *  
  
  #attr(fpl,"gradient") <- meangrad  
  fpl  
}  
  
## read in the data  
  
thedata <- read.table("pk.dat.txt")  
colnames(thedata) <- c("id","gender","creatinel","weight","age","conc","time")  
  
library(ggplot2)  
# Make the gender and id variables factors for use with ggplot  
thedata <- within(thedata, { id <- factor(id)})  
# First create the basic plot object  
pp <- ggplot(thedata,aes(x=time,y=conc,group=id))  
pp + geom_line()
```



```
##### Run some tests to determine initial values for parameters

earlyindicator = rep(c(rep(1,7), rep(0,6)), 100) * 1:1300
earlyindicator = earlyindicator[earlyindicator != 0]
lateindicator = rep(c(rep(0,7), rep(1,6)), 100) * 1:1300
lateindicator = lateindicator[lateindicator != 0]
earlydat = thedat[earlyindicator,]
latedat = thedat[lateindicator,]

logearlyconc = log(earlydat$conc)
loglateconc = log(latedat$conc)

fti= 0:99*13
avgconcs = numeric(13)
for(i in 1:13){
  avgconcs[i] = mean(thedat$conc[fti+i])
}

meanmodel = function(t, ke = .15, ka=1, V = 1){
  return(ka*200/(V*(ka-ke))*(exp(-ke*t) - exp(-ka*t)))
}

timevec = c(.25, .5, .75, 1, 1.25, 1.5, 3, 6, 9, 12, 18, 24, 36)

##### Get preliminary estimates for coefficients by linear regression
```

```

kaEst = lm(logearlyconc ~ earlydat$time)$coefficients[2]
keEst = -lm(loglateconc ~ latedat$time)$coefficients[2]
AtEst = kaEst * 200 * 1 / (kaEst - keEst) * (exp(-timevec * keEst) - exp(-timevec * kaEst))
VEst = AtEst / avgconcs
CEst = keEst * VEst

```

```

j=12
startvalsnocov = c(log(kaEst), log(CEst[j]), log(VEst[j]))

```

#Fit model with no covariates

```

pk.mlfit.nocov <- nlme(conc ~ meanfunc(time,b1,b2,b3),
                      fixed=list(b1 ~ 1, b2 ~ 1, b3 ~ 1),
                      random=list(b1 ~ 1, b2 ~ 1, b3 ~ 1),
                      groups = ~id,
                      data=thedata,
                      start=list(fixed=startvalsnocov),
                      method="ML",verbose=TRUE,weights=varPower(1.0))

```

```

##
## **Iteration 1
## LME step: Loglik: 2249.24 , nlm iterations: 40
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -1.0031411 -1.4654784 -1.0344586  0.2546465 -0.2906487 -0.1277048
## varStruct parameters:
##      power
## 0.7149398
##
## PNLs step: RSS = 8.958051
## fixed effects:-0.48272  3.44384  5.45838
## iterations: 7
##
## Convergence:
##      fixed      reStruct      varStruct
## 0.6117078 100.5950967  0.3987192
##
## **Iteration 2
## LME step: Loglik: 2621.275 , nlm iterations: 45
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.77517755 -0.90656015 -1.15784626 -0.02259676 -0.05521798 -0.46295488
## varStruct parameters:
##      power
## 0.8375289
##
## PNLs step: RSS = 10.82172
## fixed effects:-0.483042  3.45228  5.46046
## iterations: 5
##
## Convergence:
##      fixed      reStruct      varStruct
## 0.002446811 0.933178548 0.146370060
##

```



```

## **Iteration 3
## LME step: Loglik: 2635.23 , nlm iterations: 37
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.73201445 -0.87893145 -1.12235074 -0.01883306 -0.06459777 -0.47228799
## varStruct parameters:
##      power
## 0.8650705
##
## PNLs step: RSS = 11.69821
## fixed effects:-0.484726 3.45241 5.45925
## iterations: 5
##
## Convergence:
##      fixed reStruct varStruct
## 0.00347385 0.06877292 0.03183731
##
## **Iteration 4
## LME step: Loglik: 2628.234 , nlm iterations: 42
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.76375500 -0.91105980 -1.14995180 -0.01544228 -0.06508854 -0.45717844
## varStruct parameters:
##      power
## 0.8414049
##
## PNLs step: RSS = 11.0237
## fixed effects:-0.48533 3.45229 5.45864
## iterations: 4
##
## Convergence:
##      fixed reStruct varStruct
## 0.001245987 0.241534813 0.028126200
##
## **Iteration 5
## LME step: Loglik: 2631.01 , nlm iterations: 38
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.75311536 -0.90070059 -1.14094788 -0.01637022 -0.06527989 -0.46182283
## varStruct parameters:
##      power
## 0.8493787
##
## PNLs step: RSS = 11.24622
## fixed effects:-0.484934 3.45236 5.45899
## iterations: 3
##
## Convergence:
##      fixed reStruct varStruct
## 0.0008166348 0.0671635981 0.0093878219
##
## **Iteration 6
## LME step: Loglik: 2630.224 , nlm iterations: 35
## reStruct parameters:

```

```

##          id1          id2          id3          id4          id5          id6
## -0.75613137 -0.90365627 -1.14343913 -0.01603086 -0.06531787 -0.46047016
## varStruct parameters:
##      power
## 0.8471673
##
## PNLs step: RSS = 11.18422
## fixed effects:-0.485104 3.45233 5.45885
## iterations: 2
##
## Convergence:
##      fixed      reStruct      varStruct
## 0.000349830 0.025726040 0.002610364
##
## **Iteration 7
## LME step: Loglik: 2630.364 , nlm iterations: 28
## reStruct parameters:
##          id1          id2          id3          id4          id5          id6
## -0.75564335 -0.90319263 -1.14306039 -0.01610195 -0.06529428 -0.46068249
## varStruct parameters:
##      power
## 0.8475135
##
## PNLs step: RSS = 11.19383
## fixed effects:-0.485104 3.45233 5.45885
## iterations: 1
##
## Convergence:
##      fixed      reStruct      varStruct
## 0.0000000000 0.0050557270 0.0004083988
##
## **Iteration 8
## LME step: Loglik: 2630.364 , nlm iterations: 2
## reStruct parameters:
##          id1          id2          id3          id4          id5          id6
## -0.75564194 -0.90319245 -1.14306037 -0.01610155 -0.06529526 -0.46068203
## varStruct parameters:
##      power
## 0.8475138
##
## PNLs step: RSS = 11.19384
## fixed effects:-0.485104 3.45233 5.45885
## iterations: 1
##
## Convergence:
##      fixed      reStruct      varStruct
## 0.000000e+00 2.677760e-06 3.977199e-07

```

```
summary(pk.mlfit.nocov)
```

```

## Nonlinear mixed-effects model fit by maximum likelihood
## Model: conc ~ meanfunc(time, b1, b2, b3)
## Data: thedat
##          AIC          BIC      logLik

```

```

##      -5238.728 -5181.857 2630.364
##
## Random effects:
## Formula: list(b1 ~ 1, b2 ~ 1, b3 ~ 1)
## Level: id
## Structure: General positive-definite, Log-Cholesky parametrization
##          StdDev      Corr
## b1      0.20438374 b1      b2
## b2      0.40232911 0.230
## b3      0.29103319 0.253 0.822
## Residual 0.09279356
##
## Variance function:
## Structure: Power of variance covariate
## Formula: ~fitted(.)
## Parameter estimates:
##      power
## 0.8475138
## Fixed effects: list(b1 ~ 1, b2 ~ 1, b3 ~ 1)
##          Value Std.Error   DF  t-value p-value
## b1 -0.485104 0.02319269 1198 -20.91625      0
## b2  3.452334 0.04049295 1198  85.25764      0
## b3  5.458849 0.03001845 1198 181.84979      0
## Correlation:
##      b1      b2
## b2 0.229
## b3 0.312 0.812
##
## Standardized Within-Group Residuals:
##          Min          Q1          Med          Q3          Max
## -3.43301043 -0.56493844  0.01096632  0.52713177  5.47351505
##
## Number of Observations: 1300
## Number of Groups: 100

startvalsallcov = c(pk.mlfit.nocov$coefficients$fixed[1], rep(0, 4), pk.mlfit.nocov$coefficients$fixed[

pk.mlfit.allcov <- nlme(conc ~ meanfunc(time,b1,b2,b3),
                        fixed=list(b1 ~ 1 + gender + weight + age + creatinecl, b2 ~ 1 + gender + weight + age + creatinecl, b3 ~ 1 + gender + weight + age + creatinecl),
                        random=list(b1 ~ 1, b2 ~ 1, b3 ~ 1),
                        groups = ~id,
                        data=thedata,
                        start=list(fixed=startvalsallcov),
                        method="ML",verbose=TRUE,weights=varPower(1.0))

##
## **Iteration 1
## LME step: Loglik: 2268.033 , nlm iterations: 42
## reStruct parameters:
##          id1          id2          id3          id4          id5          id6
## -1.01541542 -1.52010200 -1.03983617  0.14262889 -0.34181764 -0.08433866
## varStruct parameters:
##      power

```

```

## 0.5907147
##
## PNLs step: RSS = 7.363099
## fixed effects:-0.486255 0.0144356 -0.000950258 -0.00130692 0.00143039 2.6012 0.0981532 0.011
## iterations: 7
##
## Convergence:
## fixed reStruct varStruct
## 1.0000000 20.7001236 0.6928647
##
## **Iteration 2
## LME step: Loglik: 2665.6 , nlm iterations: 39
## reStruct parameters:
## id1 id2 id3 id4 id5 id6
## -0.70232655 -0.88818557 -0.78644188 -0.03032062 -0.17841065 -0.45191247
## varStruct parameters:
## power
## 0.8293571
##
## PNLs step: RSS = 10.61664
## fixed effects:-0.477282 0.0281534 -0.00108117 -0.00103586 0.00124316 2.60621 0.101788 0.0115
## iterations: 5
##
## Convergence:
## fixed reStruct varStruct
## 0.7725350 1.0944729 0.2877439
##
## **Iteration 3
## LME step: Loglik: 2681.85 , nlm iterations: 29
## reStruct parameters:
## id1 id2 id3 id4 id5 id6
## -0.65381845 -0.85094003 -0.74033604 -0.02722924 -0.19307740 -0.46295412
## varStruct parameters:
## power
## 0.8649241
##
## PNLs step: RSS = 11.70103
## fixed effects:-0.489911 0.0274273 -0.000950271 -0.000950569 0.00119254 2.60372 0.101813 0.01
## iterations: 5
##
## Convergence:
## fixed reStruct varStruct
## 0.13774809 0.08228294 0.04112155
##
## **Iteration 4
## LME step: Loglik: 2675.433 , nlm iterations: 34
## reStruct parameters:
## id1 id2 id3 id4 id5 id6
## -0.68313661 -0.88202986 -0.76731289 -0.02376757 -0.19045409 -0.44709549
## varStruct parameters:
## power
## 0.8423049
##
## PNLs step: RSS = 11.05475

```

```

## fixed effects:-0.487128 0.0287518 -0.00102395 -0.000962328 0.00121536 2.60428 0.10186 0.0116
## iterations: 4
##
## Convergence:
## fixed reStruct varStruct
## 0.07195877 0.13593542 0.02685400
##
## **Iteration 5
## LME step: Loglik: 2678.029 , nlm iterations: 33
## reStruct parameters:
## id1 id2 id3 id4 id5 id6
## -0.67367231 -0.87251861 -0.75891017 -0.02461294 -0.19173046 -0.45152745
## varStruct parameters:
## power
## 0.8496543
##
## PNLs step: RSS = 11.25996
## fixed effects:-0.487867 0.028398 -0.00100028 -0.000957893 0.00120695 2.6042 0.101867 0.01161
## iterations: 3
##
## Convergence:
## fixed reStruct varStruct
## 0.023666144 0.034248684 0.008649956
##
## **Iteration 6
## LME step: Loglik: 2677.302 , nlm iterations: 24
## reStruct parameters:
## id1 id2 id3 id4 id5 id6
## -0.67634871 -0.87526680 -0.76129713 -0.02430634 -0.19146491 -0.45017779
## varStruct parameters:
## power
## 0.8475955
##
## PNLs step: RSS = 11.20214
## fixed effects:-0.487758 0.0284696 -0.00100636 -0.000958409 0.00120904 2.60421 0.101857 0.011
## iterations: 2
##
## Convergence:
## fixed reStruct varStruct
## 0.006045316 0.013491019 0.002429033
##
## **Iteration 7
## LME step: Loglik: 2677.43 , nlm iterations: 18
## reStruct parameters:
## id1 id2 id3 id4 id5 id6
## -0.67593157 -0.87484599 -0.76093122 -0.02436363 -0.19149004 -0.45039147
## varStruct parameters:
## power
## 0.8479117
##
## PNLs step: RSS = 11.21093
## fixed effects:-0.487758 0.0284696 -0.00100636 -0.000958409 0.00120904 2.60421 0.101857 0.011
## iterations: 1
##

```

```

## Convergence:
##      fixed      reStruct    varStruct
## 0.0000000000 0.0025159763 0.0003728685
##
## **Iteration 8
## LME step: Loglik: 2677.43 , nlm iterations: 2
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.67592933 -0.87484364 -0.76093216 -0.02436438 -0.19148924 -0.45039261
## varStruct parameters:
##      power
## 0.847912
##
## PNLs step: RSS = 11.21094
## fixed effects:-0.487758 0.0284696 -0.00100636 -0.000958409 0.00120904 2.60421 0.101857 0.011
## iterations: 1
##
## Convergence:
##      fixed      reStruct    varStruct
## 0.000000e+00 2.140378e-06 4.084624e-07

```

```
summary(pk.mlfit.allcov)
```

```

## Nonlinear mixed-effects model fit by maximum likelihood
## Model: conc ~ meanfunc(time, b1, b2, b3)
## Data: thedat
##      AIC      BIC  logLik
## -5308.86 -5189.947 2677.43
##
## Random effects:
## Formula: list(b1 ~ 1, b2 ~ 1, b3 ~ 1)
## Level: id
## Structure: General positive-definite, Log-Cholesky parametrization
##      StdDev      Corr
## b1.(Intercept) 0.20170259 b1.(I) b2.(I)
## b2.(Intercept) 0.30937144 0.331
## b3.(Intercept) 0.19875490 0.422 0.694
## Residual      0.09286442
##
## Variance function:
## Structure: Power of variance covariate
## Formula: ~fitted(.)
## Parameter estimates:
##      power
## 0.847912
## Fixed effects: list(b1 ~ 1 + gender + weight + age + creatinecl, b2 ~ 1 + gender +      weight + age
##      Value Std.Error  DF t-value p-value
## b1.(Intercept) -0.487758 0.18222754 1186 -2.676642 0.0075
## b1.gender      0.028470 0.05969570 1186 0.476913 0.6335
## b1.weight      -0.001006 0.00146804 1186 -0.685518 0.4932
## b1.age         -0.000958 0.00176589 1186 -0.542734 0.5874
## b1.creatinecl  0.001209 0.00125007 1186 0.967181 0.3337
## b2.(Intercept) 2.604212 0.24840173 1186 10.483871 0.0000
## b2.gender      0.101857 0.08130162 1186 1.252830 0.2105

```

```

## b2.weight      0.011610 0.00200284 1186  5.796867  0.0000
## b2.age         -0.002084 0.00240359 1186 -0.867123  0.3861
## b2.creatinecl  0.000067 0.00170249 1186  0.039143  0.9688
## b3.(Intercept) 4.568389 0.16815838 1186 27.167178  0.0000
## b3.gender      0.065694 0.05507774 1186  1.192749  0.2332
## b3.weight      0.009765 0.00135439 1186  7.209997  0.0000
## b3.age         0.001381 0.00163022 1186  0.847360  0.3970
## b3.creatinecl  0.000567 0.00115258 1186  0.492208  0.6227
## Correlation:
##               b1.(I) b1.gnd b1.wgh b1.age b1.crt b2.(I) b2.gnd b2.wgh
## b1.gender          0.444
## b1.weight         -0.627 -0.585
## b1.age            -0.504 -0.079 -0.001
## b1.creatinecl     -0.728 -0.334  0.170  0.133
## b2.(Intercept)    0.324  0.144 -0.204 -0.163 -0.236
## b2.gender         0.144  0.323 -0.189 -0.026 -0.108  0.445
## b2.weight        -0.203 -0.189  0.323  0.000  0.056 -0.628 -0.586
## b2.age           -0.163 -0.026  0.000  0.323  0.043 -0.504 -0.079 -0.001
## b2.creatinecl    -0.236 -0.108  0.056  0.043  0.324 -0.727 -0.336  0.170
## b3.(Intercept)   0.484  0.215 -0.303 -0.245 -0.353  0.681  0.302 -0.427
## b3.gender        0.215  0.485 -0.283 -0.039 -0.163  0.302  0.680 -0.398
## b3.weight       -0.303 -0.283  0.483 -0.001  0.083 -0.428 -0.398  0.680
## b3.age          -0.245 -0.039 -0.001  0.486  0.065 -0.342 -0.054  0.000
## b3.creatinecl   -0.353 -0.163  0.083  0.065  0.484 -0.495 -0.228  0.116
##               b2.age b2.crt b3.(I) b3.gnd b3.wgh b3.age
## b1.gender
## b1.weight
## b1.age
## b1.creatinecl
## b2.(Intercept)
## b2.gender
## b2.weight
## b2.age
## b2.creatinecl  0.134
## b3.(Intercept) -0.343 -0.495
## b3.gender      -0.054 -0.228  0.445
## b3.weight      0.000  0.117 -0.627 -0.586
## b3.age         0.679  0.091 -0.504 -0.079 -0.002
## b3.creatinecl  0.091  0.681 -0.728 -0.336  0.171  0.134
##
## Standardized Within-Group Residuals:
##           Min           Q1           Med           Q3           Max
## -3.41108540 -0.55708770  0.01351706  0.53430266  5.46715838
##
## Number of Observations: 1300
## Number of Groups: 100

```

```
startvalsweight = c(pk.mlfit.nocov$coefficients$fixed[1], pk.mlfit.nocov$coefficients$fixed[2], 0, pk.m
```

```

pk.mlfit.weight <- nlme(conc ~ meanfunc(time,b1,b2,b3),
                        fixed=list(b1 ~ 1, b2 ~ 1 + weight, b3 ~ 1 + weight),
                        random=list(b1 ~ 1, b2 ~ 1, b3 ~ 1),
                        groups = ~id,
                        data=thedata,

```

```

start=list(fixed=startvalsweight),
method="ML",verbose=TRUE,weights=varPower(1.0))

```

```

##
## **Iteration 1
## LME step: Loglik: 2258.247 , nlm iterations: 43
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -1.06486240 -1.54178577 -1.08404893  0.13720854 -0.33949434 -0.06856762
## varStruct parameters:
##      power
## 0.5902038
##
## PNLs step: RSS = 7.351156
## fixed effects:-0.480383  2.43517  0.013219  4.61931  0.0110009
## iterations: 7
##
## Convergence:
##      fixed  reStruct  varStruct
## 1.0000000 25.6520235 0.6943299
##
## **Iteration 2
## LME step: Loglik: 2655.592 , nlm iterations: 37
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.73299100 -0.93046622 -0.82051145 -0.03547613 -0.16681799 -0.42625336
## varStruct parameters:
##      power
## 0.8146673
##
## PNLs step: RSS = 10.22207
## fixed effects:-0.480674  2.43506  0.0133217  4.61981  0.0110259
## iterations: 6
##
## Convergence:
##      fixed  reStruct  varStruct
## 0.007707764 0.928905989 0.275527757
##
## **Iteration 3
## LME step: Loglik: 2677.234 , nlm iterations: 36
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.66658459 -0.87425036 -0.75896084 -0.03491925 -0.18265063 -0.44540755
## varStruct parameters:
##      power
## 0.8644477
##
## PNLs step: RSS = 11.67935
## fixed effects:-0.484273  2.43786  0.0132846  4.61364  0.0110753
## iterations: 5
##
## Convergence:
##      fixed  reStruct  varStruct

```



```

## 0.00743096 0.11304204 0.05758639
##
## **Iteration 4
## LME step: Loglik: 2669.984 , nlm iterations: 35
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.69954459 -0.90856259 -0.78874621 -0.03072743 -0.18023673 -0.42856056
## varStruct parameters:
##      power
## 0.8393597
##
## PNLs step: RSS = 10.96609
## fixed effects:-0.485189 2.43664 0.0132984 4.61408 0.0110584
## iterations: 4
##
## Convergence:
##      fixed      reStruct      varStruct
## 0.001887709 0.128486759 0.029889435
##
## **Iteration 5
## LME step: Loglik: 2672.958 , nlm iterations: 31
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.68872183 -0.89790333 -0.77931202 -0.03176828 -0.18153938 -0.43330456
## varStruct parameters:
##      power
## 0.8476641
##
## PNLs step: RSS = 11.19637
## fixed effects:-0.484806 2.43711 0.0132931 4.61395 0.0110645
## iterations: 3
##
## Convergence:
##      fixed      reStruct      varStruct
## 0.0007905284 0.0328954491 0.0097968702
##
## **Iteration 6
## LME step: Loglik: 2672.149 , nlm iterations: 33
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.69173372 -0.90092583 -0.78194614 -0.03140252 -0.18129066 -0.43187782
## varStruct parameters:
##      power
## 0.8453865
##
## PNLs step: RSS = 11.13274
## fixed effects:-0.484983 2.43699 0.0132943 4.61393 0.0110629
## iterations: 2
##
## Convergence:
##      fixed      reStruct      varStruct
## 0.0003657277 0.0125986687 0.0026942279
##
## **Iteration 7

```

```

## LME step: Loglik: 2672.287 , nlm iterations: 18
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.69127933 -0.90047974 -0.78155753 -0.03146753 -0.18131062 -0.43209610
## varStruct parameters:
##      power
## 0.8457216
##
## PNLs step: RSS = 11.142
## fixed effects:-0.484983 2.43699 0.0132943 4.61393 0.0110629
## iterations: 1
##
## Convergence:
##      fixed      reStruct      varStruct
## 0.0000000000 0.0022324538 0.0003962655
##
## **Iteration 8
## LME step: Loglik: 2672.287 , nlm iterations: 2
## reStruct parameters:
##      id1      id2      id3      id4      id5      id6
## -0.69127703 -0.90047912 -0.78155857 -0.03146802 -0.18131046 -0.43209563
## varStruct parameters:
##      power
## 0.845722
##
## PNLs step: RSS = 11.14201
## fixed effects:-0.484983 2.43699 0.0132943 4.61393 0.0110629
## iterations: 1
##
## Convergence:
##      fixed      reStruct      varStruct
## 0.000000e+00 1.870457e-06 4.322965e-07

```

```
summary(pk.mlfitt.weight)
```

```

## Nonlinear mixed-effects model fit by maximum likelihood
## Model: conc ~ meanfunc(time, b1, b2, b3)
## Data: thedat
##      AIC      BIC      logLik
## -5318.575 -5251.363 2672.287
##
## Random effects:
## Formula: list(b1 ~ 1, b2 ~ 1, b3 ~ 1)
## Level: id
## Structure: General positive-definite, Log-Cholesky parametrization
##      StdDev      Corr
## b1      0.2046474 b1      b2.(I)
## b2.(Intercept) 0.3133002 0.342
## b3.(Intercept) 0.2022724 0.424 0.686
## Residual      0.0925785
##
## Variance function:
## Structure: Power of variance covariate
## Formula: ~fitted(.)

```

```
## Parameter estimates:
## power
## 0.845722
## Fixed effects: list(b1 ~ 1, b2 ~ 1 + weight, b3 ~ 1 + weight)
##               Value Std.Error   DF   t-value p-value
## b1            -0.484983 0.02323909 1196 -20.86928    0
## b2.(Intercept)  2.436994 0.12187255 1196  19.99625    0
## b2.weight       0.013294 0.00154094 1196   8.62739    0
## b3.(Intercept)  4.613928 0.07712534 1196  59.82376    0
## b3.weight       0.011063 0.00097082 1196  11.39549    0
## Correlation:
##           b1      b2.(I) b2.wgh b3.(I)
## b2.(Intercept)  0.087
## b2.weight      -0.001 -0.966
## b3.(Intercept)  0.133  0.625 -0.597
## b3.weight       0.002 -0.599  0.621 -0.960
##
## Standardized Within-Group Residuals:
##           Min           Q1           Med           Q3           Max
## -3.465067229 -0.558355887  0.009588077  0.538324927  5.525139163
##
## Number of Observations: 1300
## Number of Groups: 100
```

```
anova(pk.mlfit.nocov, pk.mlfit.allcov, pk.mlfit.weight)
```

```
##           Model df          AIC          BIC   logLik   Test  L.Ratio
## pk.mlfit.nocov    1 11 -5238.728 -5181.857 2630.364
## pk.mlfit.allcov    2 23 -5308.860 -5189.947 2677.430 1 vs 2 94.13160
## pk.mlfit.weight    3 13 -5318.575 -5251.363 2672.287 2 vs 3 10.28504
##
##           p-value
## pk.mlfit.nocov
## pk.mlfit.allcov <.0001
## pk.mlfit.weight 0.4159
```

```
D = diag(c(0.20464741, 0.31330024, 0.20227235)) %*% matrix(c(1,0.342,0.424,0.342,1,0.686,0.424,0.686,1),
```

```
#####
```

```
##### Longitudinal study of nail growth
```

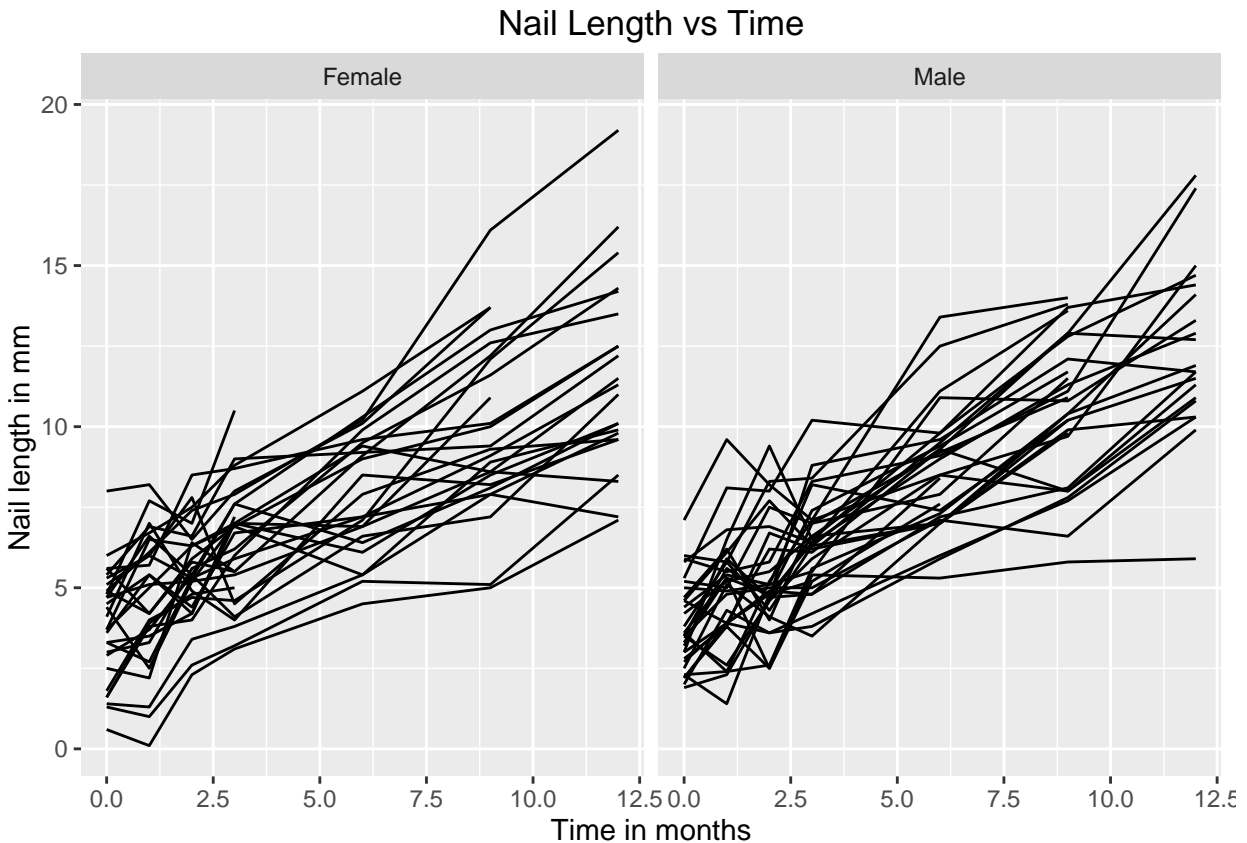
```
#####
```

```
thedata <- read.table("naillength.dat.txt")
colnames(thedata) <- c("id", "gender", "weight", "age", "time", "length")
thedata <- within(thedata, { id <- factor(id)
                             gender <- factor(gender, levels=0:1, labels=c("Female", "Male"))
                             })
```

```
# First create the basic plot object
```

```
pp <- ggplot(thedata, aes(x=time, y=length, group=id))
```

```
pp + geom_line() + facet_grid(. ~ gender) + labs(title = "Nail Length vs Time") + xlab("Time in months")
```



```
# create factors

pid <- factor(thedat$id)
gender <- factor(thedat$gender)

nl.nocov <- lme(length ~ -1 + time, random = ~ time | pid,
                data=thedat, method="ML")
summary(nl.nocov)

## Linear mixed-effects model fit by maximum likelihood
## Data: thedat
##      AIC      BIC    logLik
## 1493.878 1513.708 -741.9388
##
## Random effects:
## Formula: ~time | pid
## Structure: General positive-definite, Log-Cholesky parametrization
##              StdDev   Corr
## (Intercept) 4.2274859 (Intr)
## time        0.3227157 -0.727
## Residual    0.9957359
##
## Fixed effects: length ~ -1 + time
##              Value Std.Error DF t-value p-value
## time 0.9396756 0.03159099 330 29.74505      0
```

```
##
## Standardized Within-Group Residuals:
##      Min      Q1      Med      Q3      Max
## -2.3238851 -0.55329922  0.04756818  0.56878415  2.75891381
##
## Number of Observations: 390
## Number of Groups: 60
```

#This model has -1 so as to avoid fitting an intercept (delta model) it has a separate slope and intercept for boys and girls and has a random effect for each

```
nl.a <- lme(length ~ -1 + gender + time : gender, random = ~ time | pid,
            data=thedata, method="ML")
summary(nl.a)
```

```
## Linear mixed-effects model fit by maximum likelihood
## Data: thedat
##      AIC      BIC    logLik
## 1371.01 1402.739 -677.5048
##
## Random effects:
## Formula: ~time | pid
## Structure: General positive-definite, Log-Cholesky parametrization
##           StdDev   Corr
## (Intercept) 1.3478089 (Intr)
## time        0.2225579 -0.236
## Residual    0.9971829
##
## Fixed effects: length ~ -1 + gender + time:gender
##           Value Std.Error DF t-value p-value
## genderFemale  4.046242 0.27457033  58 14.73663      0
## genderMale    3.972998 0.26566131  58 14.95513      0
## genderFemale:time 0.672976 0.04783484 329 14.06875      0
## genderMale:time   0.741600 0.04539693 329 16.33591      0
## Correlation:
##           gndrFm gndrMl gndrF:
## genderMale      0.000
## genderFemale:time -0.323  0.000
## genderMale:time   0.000 -0.326  0.000
##
## Standardized Within-Group Residuals:
##      Min      Q1      Med      Q3      Max
## -2.246666819 -0.557162986  0.004776805  0.529919427  2.809136452
##
## Number of Observations: 390
## Number of Groups: 60
```

Full model excluding metabolite

```
nl.b <- lme(length ~ -1 + gender + age + time : gender + age*time, random = ~ time | pid,
            data=thedata, method="ML")
summary(nl.b)
```

```
## Linear mixed-effects model fit by maximum likelihood
## Data: thedat
```

```

##          AIC          BIC      logLik
##    1374.58 1414.242 -677.2901
##
## Random effects:
## Formula: ~time | pid
## Structure: General positive-definite, Log-Cholesky parametrization
##           StdDev      Corr
## (Intercept) 1.3434113 (Intr)
## time         0.2226492 -0.238
## Residual     0.9970618
##
## Fixed effects: length ~ -1 + gender + age + time:gender + age * time
##           Value Std.Error DF   t-value p-value
## genderFemale  4.418519 0.7247842  57  6.096324  0.0000
## genderMale    4.352784 0.7323249  57  5.943788  0.0000
## age          -0.008059 0.0144880  57 -0.556256  0.5802
## time          0.689265 0.1284630 328  5.365476  0.0000
## genderMale:time 0.068720 0.0661421 328  1.038971  0.2996
## age:time      -0.000346 0.0025423 328 -0.136129  0.8918
## Correlation:
##           gndrFm gndrMl age      time  gndrM:
## genderMale      0.862
## age             -0.925 -0.932
## time            -0.331 -0.284  0.305
## genderMale:time 0.087 -0.084  0.003 -0.262
## age:time        0.308  0.307 -0.330 -0.928 -0.009
##
## Standardized Within-Group Residuals:
##           Min           Q1           Med           Q3           Max
## -2.244635971 -0.555468512  0.003139146  0.539688293  2.824643567
##
## Number of Observations: 390
## Number of Groups: 60

```

```

nl.c <- lme(length ~ -1 + gender + time : gender, random = ~ time | pid,
            weights = varIdent(form = ~ 1 | gender),
            data=thedata, method="ML")
summary(nl.c)

```

```

## Linear mixed-effects model fit by maximum likelihood
## Data: thedat
##          AIC      BIC      logLik
##    1372.505 1408.2 -677.2526
##
## Random effects:
## Formula: ~time | pid
## Structure: General positive-definite, Log-Cholesky parametrization
##           StdDev      Corr
## (Intercept) 1.3500250 (Intr)
## time         0.2232867 -0.237
## Residual     0.9648129
##
## Variance function:
## Structure: Different standard deviations per stratum

```

```
## Formula: ~1 | gender
## Parameter estimates:
##      Female      Male
## 1.000000 1.062505
## Fixed effects: length ~ -1 + gender + time:gender
##              Value Std.Error DF t-value p-value
## genderFemale    4.044563 0.27357759 58 14.78397      0
## genderMale      3.973412 0.26722545 58 14.86914      0
## genderFemale:time 0.674170 0.04768902 329 14.13679      0
## genderMale:time   0.741423 0.04576219 329 16.20165      0
## Correlation:
##              gndrFm gndrMl gndrF:
## genderMale          0.000
## genderFemale:time -0.319 0.000
## genderMale:time    0.000 -0.330 0.000
##
## Standardized Within-Group Residuals:
##              Min          Q1          Med          Q3          Max
## -2.203916666 -0.562975781 -0.005552194  0.537041253  2.737012797
##
## Number of Observations: 390
## Number of Groups: 60
```

```
# Full model excluding metabolite
```

```
nl.d <- lme(length ~ -1 + gender + age + time : gender + age*time, random = ~ time | pid,
            weights = varIdent(form = ~ 1 | gender),
            data=thedata, method="ML")
summary(nl.d)
```

```
## Linear mixed-effects model fit by maximum likelihood
## Data: thedat
##      AIC      BIC    logLik
## 1376.064 1419.691 -677.0318
##
## Random effects:
## Formula: ~time | pid
## Structure: General positive-definite, Log-Cholesky parametrization
##              StdDev Corr
## (Intercept) 1.3454118 (Intr)
## time        0.2233892 -0.239
## Residual    0.9643318
##
## Variance function:
## Structure: Different standard deviations per stratum
## Formula: ~1 | gender
## Parameter estimates:
##      Female      Male
## 1.000000 1.063286
## Fixed effects: length ~ -1 + gender + age + time:gender + age * time
##              Value Std.Error DF t-value p-value
## genderFemale    4.422322 0.7247871 57 6.101546 0.0000
## genderMale      4.358808 0.7333014 57 5.944088 0.0000
## age             -0.008178 0.0144977 57 -0.564077 0.5749
## time             0.690757 0.1285997 328 5.371368 0.0000
```

```
## genderMale:time 0.067344 0.0662922 328 1.015860 0.3104
## age:time -0.000352 0.0025477 328 -0.138291 0.8901
## Correlation:
##          gndrFm gndrMl age    time  gndrM:
## genderMale      0.862
## age             -0.926 -0.931
## time            -0.331 -0.284  0.306
## genderMale:time  0.085 -0.086  0.003 -0.259
## age:time         0.309  0.307 -0.330 -0.928 -0.010
##
## Standardized Within-Group Residuals:
##          Min          Q1          Med          Q3          Max
## -2.201289451 -0.558955498 -0.007791489  0.535000910  2.752131017
##
## Number of Observations: 390
## Number of Groups: 60
```

```
nl.e <- lme(length ~ -1 + gender + time : gender, random = ~ time | pid,
            correlation=corExp(form = ~ time | pid, nugget=TRUE),
            data=thedata, method="ML")
summary(nl.e)
```

```
## Linear mixed-effects model fit by maximum likelihood
## Data: thedat
##      AIC      BIC    logLik
## 1375.01 1414.671 -677.5048
##
## Random effects:
## Formula: ~time | pid
## Structure: General positive-definite, Log-Cholesky parametrization
##          StdDev   Corr
## (Intercept) 1.3478090 (Intr)
## time        0.2225579 -0.236
## Residual    0.9971829
##
## Correlation Structure: Exponential spatial correlation
## Formula: ~time | pid
## Parameter estimate(s):
##      range    nugget
## 0.05815461 0.10123621
## Fixed effects: length ~ -1 + gender + time:gender
##          Value Std.Error DF t-value p-value
## genderFemale  4.046242 0.27457034  58 14.73663      0
## genderMale    3.972998 0.26566133  58 14.95512      0
## genderFemale:time 0.672976 0.04783484 329 14.06875      0
## genderMale:time  0.741600 0.04539693 329 16.33591      0
## Correlation:
##          gndrFm gndrMl gndrF:
## genderMale      0.000
## genderFemale:time -0.323  0.000
## genderMale:time   0.000 -0.326  0.000
##
## Standardized Within-Group Residuals:
##          Min          Q1          Med          Q3          Max
```



```
## -2.246666779 -0.557162965 0.004776746 0.529919436 2.809136524
##
## Number of Observations: 390
## Number of Groups: 60
```

```
# Full model excluding metabolite
nl.f <- lme(length ~ -1 + gender + age + time : gender + age*time, random = ~ time | pid,
            correlation=corExp(form = ~ time | pid, nugget=TRUE),
            data=thedata, method="ML")
summary(nl.f)
```

```
## Linear mixed-effects model fit by maximum likelihood
## Data: thedat
##      AIC      BIC    logLik
## 1378.58 1426.174 -677.2901
##
## Random effects:
## Formula: ~time | pid
## Structure: General positive-definite, Log-Cholesky parametrization
##           StdDev   Corr
## (Intercept) 1.3434114 (Intr)
## time         0.2226492 -0.238
## Residual     0.9970618
##
## Correlation Structure: Exponential spatial correlation
## Formula: ~time | pid
## Parameter estimate(s):
##      range      nugget
## 0.05843503 0.10112712
## Fixed effects: length ~ -1 + gender + age + time:gender + age * time
##           Value Std.Error DF   t-value p-value
## genderFemale    4.418519 0.7247843 57  6.096324 0.0000
## genderMale      4.352784 0.7323250 57  5.943788 0.0000
## age             -0.008059 0.0144880 57 -0.556256 0.5802
## time            0.689265 0.1284630 328  5.365475 0.0000
## genderMale:time  0.068720 0.0661421 328  1.038971 0.2996
## age:time        -0.000346 0.0025423 328 -0.136129 0.8918
## Correlation:
##           gndrFm gndrMl age    time  gndrM:
## genderMale      0.862
## age            -0.925 -0.932
## time           -0.331 -0.284  0.305
## genderMale:time 0.087 -0.084  0.003 -0.262
## age:time        0.308  0.307 -0.330 -0.928 -0.009
##
## Standardized Within-Group Residuals:
##           Min           Q1           Med           Q3           Max
## -2.244635931 -0.555468491  0.003139086  0.539688285  2.824643641
##
## Number of Observations: 390
## Number of Groups: 60
```

```
## Crude approximation of clearance to be used as a surrogate for metabolite availability
appxC1 = exp(2.436994 + 0.013294 * thedat$weight)
```

```
# Full model including metabolite
```

```
nl.g <- lme(length ~ -1 + gender + age + time : gender + age * time + appxC1 : time, random = ~ time | pid,
            data=thedata, method="ML")
summary(nl.g)
```

```
## Linear mixed-effects model fit by maximum likelihood
```

```
## Data: thedat
```

```
##      AIC      BIC    logLik
```

```
## 1373.377 1417.004 -675.6883
```

```
##
```

```
## Random effects:
```

```
## Formula: ~time | pid
```

```
## Structure: General positive-definite, Log-Cholesky parametrization
```

```
##      StdDev    Corr
```

```
## (Intercept) 1.3418440 (Intr)
```

```
## time      0.2227779 -0.321
```

```
## Residual    0.9973908
```

```
##
```

```
## Fixed effects: length ~ -1 + gender + age + time:gender + age * time + appxC1:time
```

```
##      Value Std.Error DF   t-value p-value
```

```
## genderFemale    4.414879 0.7250524  57  6.089048  0.0000
```

```
## genderMale     4.360922 0.7325912  57  5.952736  0.0000
```

```
## age            -0.008063 0.0144932  57 -0.556324  0.5802
```

```
## time           0.423954 0.1894814 327  2.237444  0.0259
```

```
## genderMale:time -0.032479 0.0855188 327 -0.379785  0.7044
```

```
## age:time       -0.000610 0.0025509 327 -0.239276  0.8110
```

```
## time:appxC1     0.009954 0.0052791 327  1.885582  0.0602
```

```
## Correlation:
```

```
##      gndrFm gndrMl age    time  gndrM: age:tm
```

```
## genderMale    0.862
```

```
## age          -0.925 -0.932
```

```
## time         -0.265 -0.234  0.246
```

```
## genderMale:time 0.083 -0.082  0.002  0.327
```

```
## age:time       0.369  0.367 -0.395 -0.580  0.034
```

```
## time:appxC1    -0.006  0.004  0.002 -0.734 -0.633 -0.066
```

```
##
```

```
## Standardized Within-Group Residuals:
```

```
##      Min      Q1      Med      Q3      Max
```

```
## -2.20165385 -0.56909639 -0.01416156  0.54643099  2.82940555
```

```
##
```

```
## Number of Observations: 390
```

```
## Number of Groups: 60
```

```
nl.h <- lme(length ~ -1 + gender + age + time : gender + age * time + appxC1 : time, random = ~ time | pid,
            weights = varIdent(form = ~ 1 | gender),
            data=thedata, method="ML")
summary(nl.h)
```

```
## Linear mixed-effects model fit by maximum likelihood
```

```
## Data: thedat
##      AIC      BIC    logLik
## 1374.807 1422.401 -675.4035
##
## Random effects:
## Formula: ~time | pid
## Structure: General positive-definite, Log-Cholesky parametrization
##      StdDev    Corr
## (Intercept) 1.3439991 (Intr)
## time        0.2233264 -0.323
## Residual    0.9631883
##
## Variance function:
## Structure: Different standard deviations per stratum
## Formula: ~1 | gender
## Parameter estimates:
##   Female    Male
## 1.000000 1.066542
## Fixed effects: length ~ -1 + gender + age + time:gender + age * time + appxC1:time
##      Value Std.Error DF   t-value p-value
## genderFemale    4.419705 0.7250915  57   6.095376  0.0000
## genderMale      4.368246 0.7336612  57   5.954037  0.0000
## age             -0.008202 0.0145043  57  -0.565497  0.5740
## time            0.422186 0.1899439 327   2.222689  0.0269
## genderMale:time -0.035052 0.0856943 327  -0.409038  0.6828
## age:time        -0.000613 0.0025543 327  -0.240146  0.8104
## time:appxC1     0.010064 0.0052923 327   1.901557  0.0581
## Correlation:
##      gndrFm gndrMl age    time  gndrM: age:tm
## genderMale    0.862
## age          -0.926 -0.931
## time         -0.265 -0.234  0.247
## genderMale:time 0.081 -0.085  0.003  0.330
## age:time       0.370  0.367 -0.396 -0.580  0.033
## time:appxC1    -0.005  0.005  0.002 -0.736 -0.633 -0.065
##
## Standardized Within-Group Residuals:
##      Min      Q1      Med      Q3      Max
## -2.15640845 -0.57756426 -0.00716516  0.52977255  2.75309564
##
## Number of Observations: 390
## Number of Groups: 60
```

```
nl.i <- lme(length ~ -1 + gender + age + time : gender + age * time + appxC1 : time, random = ~ time | pid,
            correlation=corExp(form = ~ time | pid, nugget=TRUE),
            data=thedat, method="ML")
summary(nl.i)
```

```
## Linear mixed-effects model fit by maximum likelihood
## Data: thedat
##      AIC      BIC    logLik
## 1377.377 1428.937 -675.6883
##
## Random effects:
```

```
## Formula: ~time | pid
## Structure: General positive-definite, Log-Cholesky parametrization
##           StdDev   Corr
## (Intercept) 1.3418441 (Intr)
## time        0.2227780 -0.321
## Residual    0.9973908
##
## Correlation Structure: Exponential spatial correlation
## Formula: ~time | pid
## Parameter estimate(s):
##      range      nugget
## 0.05749018 0.09805924
## Fixed effects: length ~ -1 + gender + age + time:gender + age * time + appxC1:time
##           Value Std.Error DF   t-value p-value
## genderFemale    4.414879 0.7250525 57  6.089048 0.0000
## genderMale      4.360922 0.7325912 57  5.952736 0.0000
## age             -0.008063 0.0144932 57 -0.556324 0.5802
## time            0.423954 0.1894814 327  2.237444 0.0259
## genderMale:time -0.032479 0.0855188 327 -0.379785 0.7044
## age:time        -0.000610 0.0025509 327 -0.239276 0.8110
## time:appxC1     0.009954 0.0052791 327  1.885582 0.0602
## Correlation:
##           gndrFm gndrMl age    time  gndrM: age:tm
## genderMale      0.862
## age            -0.925 -0.932
## time           -0.265 -0.234  0.246
## genderMale:time 0.083 -0.082  0.002  0.327
## age:time        0.369  0.367 -0.395 -0.580  0.034
## time:appxC1    -0.006  0.004  0.002 -0.734 -0.633 -0.066
##
## Standardized Within-Group Residuals:
##           Min           Q1           Med           Q3           Max
## -2.20165381 -0.56909640 -0.01416155  0.54643099  2.82940562
##
## Number of Observations: 390
## Number of Groups: 60
```

#removing age from model

```
nl.j <- lme(length ~ -1 + gender + time : gender + appxC1 : time, random = ~ time | pid,
            correlation=corExp(form = ~ time | pid, nugget=TRUE),
            data=thedata, method="ML")
summary(nl.j)
```

```
## Linear mixed-effects model fit by maximum likelihood
## Data: thedat
##           AIC      BIC    logLik
## 1373.943 1417.571 -675.9716
##
## Random effects:
## Formula: ~time | pid
## Structure: General positive-definite, Log-Cholesky parametrization
##           StdDev   Corr
## (Intercept) 1.3464655 (Intr)
## time        0.2225287 -0.317
```

```
## Residual    0.9975915
##
## Correlation Structure: Exponential spatial correlation
## Formula: ~time | pid
## Parameter estimate(s):
##      range      nugget
## 0.05738962 0.09834403
## Fixed effects: length ~ -1 + gender + time:gender + appxC1:time
##              Value Std.Error DF   t-value p-value
## genderFemale   4.042918 0.27471583  58 14.716726  0.0000
## genderMale     3.980685 0.26583559  58 14.974235  0.0000
## genderFemale:time 0.402090 0.15406730 328  2.609836  0.0095
## genderMale:time  0.372054 0.20544946 328  1.810925  0.0711
## time:appxC1     0.009707 0.00525702 328  1.846401  0.0657
## Correlation:
##              gndrFm gndrMl gndrF: gndrM:
## genderMale         0.000
## genderFemale:time -0.112 -0.016
## genderMale:time    0.008 -0.103  0.927
## time:appxC1       -0.008  0.017 -0.951 -0.975
##
## Standardized Within-Group Residuals:
##      Min      Q1      Med      Q3      Max
## -2.204737373 -0.567344592 -0.009081296  0.537590798  2.813525029
##
## Number of Observations: 390
## Number of Groups: 60
```

It looks like one of the models with only gender works best. Try with no random effect for intercept

```
#Use anova to compare all
anova(nl.nocov, nl.a, nl.b, nl.c, nl.d, nl.e, nl.f, nl.g, nl.h, nl.i, nl.j)
```

```
##      Model df      AIC      BIC    logLik      Test  L.Ratio p-value
## nl.nocov   1  5 1493.878 1513.708 -741.9388
## nl.a       2  8 1371.009 1402.739 -677.5048  1 vs 2 128.86810 <.0001
## nl.b       3 10 1374.580 1414.242 -677.2901  2 vs 3  0.42922 0.8069
## nl.c       4  9 1372.505 1408.200 -677.2526  3 vs 4  0.07516 0.7840
## nl.d       5 11 1376.063 1419.691 -677.0318  4 vs 5  0.44162 0.8019
## nl.e       6 10 1375.009 1414.671 -677.5048  5 vs 6  0.94600 0.3307
## nl.f       7 12 1378.580 1426.174 -677.2901  6 vs 7  0.42922 0.8069
## nl.g       8 11 1373.377 1417.004 -675.6883  7 vs 8  3.20366 0.0735
## nl.h       9 12 1374.807 1422.401 -675.4035  8 vs 9  0.56954 0.4504
## nl.i      10 13 1377.377 1428.937 -675.6883  9 vs 10 0.56954 0.4504
## nl.j      11 11 1373.943 1417.571 -675.9716 10 vs 11 0.56649 0.7533
```

```
#####
##### Pilot comparative longitudinal study of disease severity
#####
```

```
thedata <- read.table("nailseverity.dat.txt")
```

```
colnames(thedat) <- c("id","gender","age","treatment","time","severity")

thedat.wide <- reshape(thedat,v.names="severity",idvar="id",
                       timevar="time",direction="wide")

prop.itraconazole <- apply(thedat.wide[thedat.wide$treatment==0,5:8],2,mean)
prop.diptroconazole <- apply(thedat.wide[thedat.wide$treatment==1,5:8],2,mean)
prop.itraconazole
```

```
## severity.0 severity.1 severity.3 severity.6
## 0.3663366 0.3564356 0.3168317 0.1782178
```

```
prop.diptroconazole
```

```
## severity.0 severity.1 severity.3 severity.6
## 0.4141414 0.3737374 0.2121212 0.1010101
```

```
library(gee)
```

```
## Warning: package 'gee' was built under R version 3.1.3
```

```
un.gee.nocovs <- gee(severity ~ time,id=id,family=binomial,
                    corstr="unstructured",scale.fix=TRUE,scale.value=1,data=thedat)
```

```
## Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
## running glm to get initial regression estimate
```

```
## (Intercept)      time
## -0.3814982 -0.2294865
```

```
summary(un.gee.nocovs)
```

```
##
## GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
## gee S-function, version 4.13 modified 98/01/27 (1998)
##
## Model:
## Link:                               Logit
## Variance to Mean Relation: Binomial
## Correlation Structure:      Unstructured
##
## Call:
## gee(formula = severity ~ time, id = id, data = thedat, family = binomial,
##      corstr = "unstructured", scale.fix = TRUE, scale.value = 1)
##
## Summary of Residuals:
##      Min      1Q   Median      3Q      Max
## -0.4012750 -0.3483801 -0.1472634  0.5987250  0.8527366
##
##
```

```

## Coefficients:
##           Estimate Naive S.E.   Naive z Robust S.E.   Robust z
## (Intercept) -0.4001552 0.13732588 -2.913910  0.13730633 -2.914325
## time        -0.2260121 0.02957116 -7.642993  0.02922738 -7.732891
##
## Estimated Scale Parameter:  1
## Number of Iterations:  3
##
## Working Correlation
##           [,1]      [,2]      [,3]      [,4]
## [1,] 1.0000000 0.6740599 0.6163817 0.4056643
## [2,] 0.6740599 1.0000000 0.6916501 0.4664574
## [3,] 0.6163817 0.6916501 1.0000000 0.5044388
## [4,] 0.4056643 0.4664574 0.5044388 1.0000000

#### Fit the model with all the covariates

un.gee.allcovs <- gee(severity ~ age + gender + time + treatment : time,id=id,family=binomial,
                      corstr="unstructured",scale.fix=TRUE,scale.value=1,data=thedata)

## Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
## running glm to get initial regression estimate

##      (Intercept)          age          gender          time time:treatment
##      -0.422607625    0.001415052   -0.042505427   -0.177774875   -0.118981105

summary(un.gee.allcovs)

##
## GEE:  GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
## gee S-function, version 4.13 modified 98/01/27 (1998)
##
## Model:
## Link:                               Logit
## Variance to Mean Relation: Binomial
## Correlation Structure:      Unstructured
##
## Call:
## gee(formula = severity ~ age + gender + time + treatment:time,
##      id = id, data = thedat, family = binomial, corstr = "unstructured",
##      scale.fix = TRUE, scale.value = 1)
##
## Summary of Residuals:
##      Min      1Q    Median      3Q      Max
## -0.4137011 -0.3327171 -0.2070889  0.5962446  0.9112556
##
##
## Coefficients:
##           Estimate Naive S.E.   Naive z Robust S.E.
## (Intercept) -0.450643141 0.447094494 -1.00793713 0.461246444
## age          0.001351144 0.009030394  0.14962182 0.009042948
## gender       -0.015592575 0.261047111 -0.05973089 0.261915866

```

```

## time          -0.157366177 0.036431439 -4.31951578 0.030420108
## time:treatment -0.159860673 0.058327763 -2.74073039 0.060380915
##               Robust z
## (Intercept)   -0.97701163
## age           0.14941411
## gender        -0.05953276
## time          -5.17309719
## time:treatment -2.64753646
##
## Estimated Scale Parameter: 1
## Number of Iterations: 4
##
## Working Correlation
##           [,1]      [,2]      [,3]      [,4]
## [1,] 1.0000000 0.6687663 0.6054534 0.4074341
## [2,] 0.6687663 1.0000000 0.6897295 0.4629248
## [3,] 0.6054534 0.6897295 1.0000000 0.4808996
## [4,] 0.4074341 0.4629248 0.4808996 1.0000000

cs.gee.allcovs <- gee(severity ~age + gender + time + treatment : time,id=id,family=binomial,
                      corstr="exchangeable",scale.fix=TRUE,scale.value=1,data=thedata)

## Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
## running glm to get initial regression estimate

##      (Intercept)          age          gender          time time:treatment
##      -0.422607625      0.001415052      -0.042505427      -0.177774875      -0.118981105

summary(cs.gee.allcovs)

##
## GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
## gee S-function, version 4.13 modified 98/01/27 (1998)
##
## Model:
## Link:                               Logit
## Variance to Mean Relation: Binomial
## Correlation Structure:      Exchangeable
##
## Call:
## gee(formula = severity ~ age + gender + time + treatment:time,
##      id = id, data = thedat, family = binomial, corstr = "exchangeable",
##      scale.fix = TRUE, scale.value = 1)
##
## Summary of Residuals:
##      Min      1Q      Median      3Q      Max
## -0.4452413 -0.3436165 -0.2085664  0.5899025  0.9153135
##
##
## Coefficients:
##              Estimate Naive S.E.      Naive z Robust S.E.
## (Intercept)  -0.550322426 0.432494390 -1.272438299 0.472041910

```



```
## age          0.003811435 0.008740177 0.436082106 0.009108054
## gender       -0.001189349 0.252238467 -0.004715178 0.267139301
## time         -0.162704446 0.033131195 -4.910913922 0.031807089
## time:treatment -0.154363195 0.055106206 -2.801194394 0.060912466
##              Robust z
## (Intercept)  -1.165833828
## age          0.418468592
## gender       -0.004452169
## time         -5.115351636
## time:treatment -2.534180666
##
## Estimated Scale Parameter: 1
## Number of Iterations: 4
##
## Working Correlation
##      [,1]      [,2]      [,3]      [,4]
## [1,] 1.0000000 0.5521763 0.5521763 0.5521763
## [2,] 0.5521763 1.0000000 0.5521763 0.5521763
## [3,] 0.5521763 0.5521763 1.0000000 0.5521763
## [4,] 0.5521763 0.5521763 0.5521763 1.0000000

iden.gee.allcovs <- gee(severity ~age + gender + time + treatment : time,id=id,family=binomial,
                        corstr="independence",scale.fix=TRUE,scale.value=1,data=thedata)

## Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
## running glm to get initial regression estimate

##      (Intercept)          age          gender          time time:treatment
##      -0.422607625    0.001415052   -0.042505427   -0.177774875   -0.118981105

summary(iden.gee.allcovs)

##
## GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
## gee S-function, version 4.13 modified 98/01/27 (1998)
##
## Model:
## Link:                               Logit
## Variance to Mean Relation: Binomial
## Correlation Structure:      Independent
##
## Call:
## gee(formula = severity ~ age + gender + time + treatment:time,
##      id = id, data = thedat, family = binomial, corstr = "independence",
##      scale.fix = TRUE, scale.value = 1)
##
## Summary of Residuals:
##      Min      1Q      Median      3Q      Max
## -0.4208442 -0.3426558 -0.1983614  0.5907597  0.9005363
##
##
## Coefficients:
```

```
##               Estimate Naive S.E.   Naive z Robust S.E.   Robust z
## (Intercept)   -0.422607625 0.28587761 -1.4782816 0.469011896 -0.9010595
## age           0.001415052 0.00559913  0.2527271 0.009208188 0.1536732
## gender        -0.042505427 0.16231773 -0.2618656 0.262699917 -0.1618022
## time          -0.177774875 0.04422220 -4.0200368 0.040092166 -4.4341549
## time:treatment -0.118981105 0.05745239 -2.0709514 0.073829863 -1.6115580
##
## Estimated Scale Parameter: 1
## Number of Iterations: 1
##
## Working Correlation
##      [,1] [,2] [,3] [,4]
## [1,]    1    0    0    0
## [2,]    0    1    0    0
## [3,]    0    0    1    0
## [4,]    0    0    0    1
```

```
### Fit the models without age or gender
```

```
un.gee.redcovs <- gee(severity ~ 1 + time + treatment : time,id=id,family=binomial,
                      corstr="unstructured",scale.fix=TRUE,scale.value=1,data=thedat)
```

```
## Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
## running glm to get initial regression estimate
```

```
##      (Intercept)           time time:treatment
##      -0.3766479      -0.1772292      -0.1200949
```

```
summary(un.gee.redcovs)
```

```
##
## GEE:  GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
## gee S-function, version 4.13 modified 98/01/27 (1998)
##
## Model:
## Link:                               Logit
## Variance to Mean Relation: Binomial
## Correlation Structure:      Unstructured
##
## Call:
## gee(formula = severity ~ 1 + time + treatment:time, id = id,
##      data = thedat, family = binomial, corstr = "unstructured",
##      scale.fix = TRUE, scale.value = 1)
##
## Summary of Residuals:
##      Min      1Q   Median      3Q      Max
## -0.4025911 -0.3291830 -0.2078446  0.5974089  0.9087025
##
##
## Coefficients:
##               Estimate Naive S.E.   Naive z Robust S.E.   Robust z
## (Intercept)   -0.3946805 0.13690026 -2.882978  0.13746352 -2.871165
```

```
## time          -0.1572144 0.03640158 -4.318890  0.03047935 -5.158064
## time:treatment -0.1599878 0.05826414 -2.745906  0.06034207 -2.651348
##
## Estimated Scale Parameter: 1
## Number of Iterations: 3
##
## Working Correlation
##      [,1]      [,2]      [,3]      [,4]
## [1,] 1.0000000 0.6683779 0.6063421 0.4070019
## [2,] 0.6683779 1.0000000 0.6895815 0.4624829
## [3,] 0.6063421 0.6895815 1.0000000 0.4805012
## [4,] 0.4070019 0.4624829 0.4805012 1.0000000
```

```
cs.gee.redcovs <- gee(severity ~ 1 + time + treatment : time,id=id,family=binomial,
                      corstr="exchangeable",scale.fix=TRUE,scale.value=1,data=thedata)
```

```
## Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
## running glm to get initial regression estimate
```

```
##      (Intercept)          time time:treatment
##      -0.3766479      -0.1772292      -0.1200949
```

```
summary(cs.gee.redcovs)
```

```
##
## GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
## gee S-function, version 4.13 modified 98/01/27 (1998)
##
## Model:
## Link:                      Logit
## Variance to Mean Relation: Binomial
## Correlation Structure:     Exchangeable
##
## Call:
## gee(formula = severity ~ 1 + time + treatment:time, id = id,
##      data = thedat, family = binomial, corstr = "exchangeable",
##      scale.fix = TRUE, scale.value = 1)
##
## Summary of Residuals:
##      Min      1Q      Median      3Q      Max
## -0.4085252 -0.3347097 -0.2065906  0.5914748  0.9064832
##
##
## Coefficients:
##      Estimate Naive S.E.   Naive z Robust S.E.  Robust z
## (Intercept)  -0.3700655 0.12725813 -2.907991  0.13952654 -2.652294
## time         -0.1625891 0.03309338 -4.913042  0.03168913 -5.130755
## time:treatment -0.1543051 0.05505800 -2.802592  0.06088107 -2.534534
##
## Estimated Scale Parameter: 1
## Number of Iterations: 3
##
```

```
## Working Correlation
##      [,1]      [,2]      [,3]      [,4]
## [1,] 1.0000000 0.5522106 0.5522106 0.5522106
## [2,] 0.5522106 1.0000000 0.5522106 0.5522106
## [3,] 0.5522106 0.5522106 1.0000000 0.5522106
## [4,] 0.5522106 0.5522106 0.5522106 1.0000000

iden.gee.redcovs <- gee(severity ~ 1 + time + treatment : time,id=id,family=binomial,
                        corstr="independence",scale.fix=TRUE,scale.value=1,data=thedata)

## Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
## running glm to get initial regression estimate

##      (Intercept)          time time:treatment
##      -0.3766479      -0.1772292      -0.1200949

summary(iden.gee.redcovs)

##
## GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
## gee S-function, version 4.13 modified 98/01/27 (1998)
##
## Model:
## Link:                      Logit
## Variance to Mean Relation: Binomial
## Correlation Structure:      Independent
##
## Call:
## gee(formula = severity ~ 1 + time + treatment:time, id = id,
##      data = thedat, family = binomial, corstr = "independence",
##      scale.fix = TRUE, scale.value = 1)
##
## Summary of Residuals:
##      Min      1Q      Median      3Q      Max
## -0.4069356 -0.3376080 -0.1915418  0.5930644  0.8966545
##
##
## Coefficients:
##              Estimate Naive S.E.   Naive z Robust S.E.  Robust z
## (Intercept)  -0.3766479 0.11030402 -3.414634  0.13894625 -2.710745
## time         -0.1772292 0.04415435 -4.013856  0.04029202 -4.398618
## time:treatment -0.1200949 0.05727127 -2.096949  0.07396441 -1.623685
##
## Estimated Scale Parameter: 1
## Number of Iterations: 1
##
## Working Correlation
##      [,1] [,2] [,3] [,4]
## [1,] 1    0    0    0
## [2,] 0    1    0    0
## [3,] 0    0    1    0
## [4,] 0    0    0    1
```

```
### There is no way to do model comparisons, but we select un.gee.redcovs as our model  
#because CS and identity correlations seem unlikely based on results of unstructured
```