Models In Epidemiology And Biostatistics
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Marginal Models With Repeated Measures

We now consider models that do not use subject specific components to address the repeated measures nature of such studies. As such, we will not be conditioning on $\boldsymbol{u}_0, \ \boldsymbol{u}_1$ ... etc and these models will all be marginal in this sense. It is useful to have the marginal/conditional distinction when comparing these two classes of models with repeated measures.
Instead of directly addressing the issue of between and within subject comparisons as we did with the conditional models, attention focusses on the consideration of the lack of independence of the residuals. We will see that in the world of marginal models, we are always discussing marginal independence as opposed to conditional independence.
A few thoughts to get us started:
1) conditional independence does not imply marginal independence
2) a regression coefficient from a conditional model does not have the same interpretation as the corresponding regression coefficient from a marginal model even when the two models use the same set of regression coefficients

And now some results when the residuals are normally distributed:
1) A conditional model with a single $\boldsymbol{u}$ and conditionally independent residuals is same as a marginal model with compound symmetry correlation structure. This is almost exactly the same as an exchangeable correlation structure. With compound symmetry the common correlation must be positive. An exchangeable correlation structure does allow for positive or negative common correlation.
2) A set of orthogonal contrasts is statistically independent if and only if residuals have an exchangeable correlation structure. One implication of this result is that a 'repeated measures' analysis of variance needs the residuals to have exchangeable correlations [not necessarily independent residuals]
3) When we have normally distributed residuals, the study of the forms of lack-of independence can be done entirely with VARiance matrices without any loss of generality.

```
. use pott.dta
. xtset subject age
. xtreg dist age sex as,pa corr(unstr)

GEE population-averaged model                   Number of obs      =       108
Group and time vars:          subject age       Number of groups   =        27
Link:                            identity       Obs per group: min =         4
Family:                          Gaussian                      avg =       4.0
Correlation:                 unstructured                      max =         4
                                                Wald chi2(3)       =    120.84
Scale parameter:                  4.90558       Prob > chi2        =    0.0000

------------------------------------------------------------------------------
        dist |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   .7881161   .0834143     9.45   0.000     .6246271    .9516052
         sex |    1.07363   1.546363     0.69   0.487    -1.957185    4.104445
          as |  -.3100221   .1306851    -2.37   0.018    -.5661602    -.053884
       _cons |   16.32362   .9870197    16.54   0.000      14.3891    18.25815
------------------------------------------------------------------------------
```

```
. xtreg dist age sex as,pa corr(ar 1)

GEE population-averaged model                   Number of obs      =       108
Group and time vars:          subject age       Number of groups   =        27
Link:                            identity       Obs per group: min =         4
Family:                          Gaussian                      avg =       4.0
Correlation:                        AR(1)                      max =         4
                                                Wald chi2(3)       =     70.82
Scale parameter:                 4.910652       Prob > chi2        =    0.0000

------------------------------------------------------------------------------
        dist |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   .7694567   .1144244     6.72   0.000      .545189    .9937243
         sex |   .7266738   2.080135     0.35   0.727    -3.350315    4.803663
          as |  -.2856919   .1792686    -1.59   0.111    -.6370518    .0656681
       _cons |   16.59461   1.327718    12.50   0.000     13.99233    19.19689
------------------------------------------------------------------------------

. xtreg dist age sex as,pa corr(exch)

GEE population-averaged model                   Number of obs      =       108
Group variable:                   subject       Number of groups   =        27
Link:                            identity       Obs per group: min =         4
Family:                          Gaussian                      avg =       4.0
Correlation:                 exchangeable                      max =         4
                                                Wald chi2(3)       =    142.05
Scale parameter:                 4.905158       Prob > chi2        =    0.0000

------------------------------------------------------------------------------
        dist |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |    .784375   .0765383    10.25   0.000     .6343626    .9343874
         sex |   1.032102   1.508864     0.68   0.494    -1.925217    3.989422
          as |  -.3048295   .1199125    -2.54   0.011    -.5398537   -.0698054
       _cons |   16.34062   .9630849    16.97   0.000     14.45301    18.22824
------------------------------------------------------------------------------
```

Now let us consider a cross over study of cerebrovascular deficiency where treatments are active (1) drug and placebo(0), respectively: the outcome indicates whether an electrocardiogram was judged abnormal (0) or normal (1).

```
. use ecg.dta
. gen tror=tr*ord
. xtlogit ecg tr ord tror,pa
GEE population-averaged model                   Number of obs      =       134
Group variable:                        id       Number of groups   =        67
Link:                               logit       Obs per group: min =         2
Family:                          binomial                      avg =       2.0
Correlation:                 exchangeable                      max =         2
                                                Wald chi2(3)       =      7.66
Scale parameter:                        1       Prob > chi2        =    0.0536

------------------------------------------------------------------------------
         ecg |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          tr |   .0870114   .5149287     0.17   0.866    -.9222302    1.096253
         ord |  -.1753529   .5056787    -0.35   0.729    -1.166465    .8157592
        tror |   1.022651   .9787989     1.04   0.296    -.8957599    2.941061
       _cons |   .6061358   .3588703     1.69   0.091     -.097237    1.309509
------------------------------------------------------------------------------
. xtlogit ecg tr ord,pa

GEE population-averaged model                   Number of obs      =       134
Group variable:                        id       Number of groups   =        67
```

```
Link:                             logit      Obs per group: min =          2
Family:                        binomial                     avg =        2.0
Correlation:               exchangeable                     max =          2
                                           Wald chi2(2)       =       7.51
Scale parameter:                      1    Prob > chi2        =     0.0234

------------------------------------------------------------------------------
         ecg |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          tr |   .5688666   .2332922     2.44   0.015     .1116222    1.026111
         ord |   .2950148   .2316903     1.27   0.203    -.1590899    .7491195
       _cons |   .3709189   .2718501     1.36   0.172    -.1618976    .9037354
------------------------------------------------------------------------------

. melogit ecg tr ord tror ||id:, intp(25)
Mixed-effects logistic regression               Number of obs      =       134
Group variable:              id                 Number of groups   =        67

                                                Obs per group: min =         2
                                                               avg =       2.0
                                                               max =         2

Integration method: mvaghermite                 Integration points =        25

                                                Wald chi2(3)       =      4.30
Log likelihood = -67.529817                     Prob > chi2        =    0.2307
------------------------------------------------------------------------------
         ecg |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          tr |   .2380711   1.626908     0.15   0.884     -2.95061    3.426752
         ord |  -.5703386   1.625077    -0.35   0.726    -3.755431    2.614754
        tror |   3.388759   3.299677     1.03   0.304    -3.078488    9.856007
       _cons |   1.985415   1.375687     1.44   0.149    -.7108822    4.681713
-------------+----------------------------------------------------------------
id           |
   var(_cons)|   24.73935   20.05961                      5.048959    121.2202
------------------------------------------------------------------------------
LR test vs. logistic regression: chibar2(01) =    27.04 Prob>=chibar2 = 0.0000

. melogit ecg tr ord ||id:, intp(25)
Mixed-effects logistic regression               Number of obs      =       134
Group variable:              id                 Number of groups   =        67

                                                Obs per group: min =         2
                                                               avg =       2.0
                                                               max =         2

Integration method: mvaghermite                 Integration points =        25

                                                Wald chi2(2)       =      4.22
Log likelihood = -68.121559                     Prob > chi2        =    0.1215
------------------------------------------------------------------------------
         ecg |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          tr |   1.872349   .9346993     2.00   0.045     .0403723    3.704326
         ord |   1.044224   .8241303     1.27   0.205    -.5710417     2.65949
       _cons |   1.193643   .9932067     1.20   0.229    -.7530063    3.140292
-------------+----------------------------------------------------------------
id           |
   var(_cons)|   24.89952   19.83645                      5.224838    118.6613
------------------------------------------------------------------------------
LR test vs. logistic regression: chibar2(01) =    27.64 Prob>=chibar2 = 0.0000
```

The marginal models here assume an exchangeable correlation structure. The snag is that our outcome is dichotomous [0=abnormal, 1=normal]. We are implicitly computing a correlation among numbers entirely made up of zeros and ones. This number has been called the ϕ coefficient. The distribution of ϕ is complicated and depends on the marginals. It is generally viewed as obsolete.

An alternate marginal model for logistic regression provides for association intra subject captured by an odds ratio. [α is the intra subject log OR] There is an implementation of this model [called Alternating Logistic Regression] in R. The code is from the late 1990's and seems to perform adequately, but not always. Here are some edited analyses.

```
> install.packages("alr", repos="http://R-Forge.R-project.org")
> library(alr)
> attach(ecg_cot)
> ecg_cot$X<-cbind(tr,ord,tror)
> summary(alr(ecg~ecg_cot$X,id=id,depm="exchangeable",ainit=0.01))

ALR:  ALTERNATING LOGISTIC REGRESSION
alr S-function, version 4.4 98/02/24

Call:
alr(formula = ecg ~ ecg_cot$X, id = id, ainit = 0.01, depmodel = "exchangeable")

Summary of Residuals:
       Min         1Q     Median         3Q        Max
-0.8235294 -0.6060606  0.1764706  0.3529412  0.3939394


Coefficients:
                 Estimate Robust S.E.   Robust z
(Intercept)    0.60613580   0.3588703  1.6890109
ecg_cot$Xtr    0.08701138   0.5149287  0.1689775
ecg_cot$Xord  -0.17535289   0.5056787 -0.3467674
ecg_cot$Xtror  1.02265075   0.9789663  1.0446231


Alpha:
   Estimate Robust S.E. Robust z
a1 3.537803   0.8200298 4.314238


Number of observations :  134
Number of Iterations   :  5

> ecg_cot$X1<-cbind(tr,ord)
> summary(alr(ecg~ecg_cot$X1,id=id,depm="exchangeable",ainit=0.01))

ALR:  ALTERNATING LOGISTIC REGRESSION
alr S-function, version 4.4 98/02/24

Call:
alr(formula = ecg ~ ecg_cot$X1, id = id, ainit = 0.01, depmodel = "exchangeable")

Summary of Residuals:
       Min         1Q     Median         3Q        Max
-0.7761458 -0.5937025  0.2238542  0.3375072  0.4062975


Coefficients:
               Estimate Robust S.E. Robust z
(Intercept)   0.3792929   0.2731244 1.388718
ecg_cot$X1tr  0.5689228   0.2335157 2.436336
ecg_cot$X1ord 0.2951299   0.2318499 1.272935


Alpha:
```

```
   Estimate Robust S.E. Robust z
a1 3.561692   0.8147993  4.37125


Number of observations :  134
Number of Iterations   :  5
```

Now let us consider an ordinal outcome study.
Costa, M.L., MacMillan, K., Halliday, D., Chester, R., Shepstone, L., Robinson, A.H.N., Donell, S.T. (2006). Randomised controlled trials of immediate weight-bearing mobilisation for rupture of the tendon Achillis. Journal of Bone and Joint Surgery (British) 88-B, 69-77.

48 participants.
Patient [a patient identifier variable]
Treat [post-surgery treatments are either immediate mobilisation in a carbon-fibre orthosis with three 1.5cm heel raises (1) or traditional plaster cast immobilisation (2)]
Time [recorded at baseline (1), six months (2) and one year (3) post-surgery]
Activity [ability to undertake usual activities post-surgery; this was scored by each patient as either no problem (1), some problem (2) or an inability (3) to perform usual activity (e.g. work, leisure, housework etc)].

Let us first consider the conditional model:

```
use achilles.dta
replace treat=treat-1
gen tt=treat*time
meologit activity treat time tt || patient:

Mixed-effects ologit regression                 Number of obs      =       125
Group variable:         patient                 Number of groups   =        48

                                                Obs per group: min =         1
                                                               avg =       2.6
                                                               max =         3

Integration method: mvaghermite                 Integration points =         7

                                                Wald chi2(3)       =     24.24
Log likelihood = -75.627446                     Prob > chi2        =    0.0000
------------------------------------------------------------------------------
    activity |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       treat |  -3.088212   1.534249    -2.01   0.044    -6.095285    -.081138
        time |  -3.723794   .9061139    -4.11   0.000    -5.499745   -1.947843
          tt |   2.288019   .9046031     2.53   0.011     .5150301    4.061009
-------------+----------------------------------------------------------------
       /cut1 |  -5.679635   1.475033    -3.85   0.000    -8.570645   -2.788624
       /cut2 |  -1.803874   1.238633    -1.46   0.145    -4.231551    .6238021
-------------+----------------------------------------------------------------
patient      |
   var(_cons)|   1.259252   1.073274                      .2369324    6.692694
------------------------------------------------------------------------------
LR test vs. ologit regression:   chibar2(01) =     3.07 Prob>=chibar2 = 0.0398
```

A comparable marginal model is available in R using the package repolr.

```
achilles <- read.csv("achilles.csv")
summary(repolr(activity~treat*time,
data=achilles,categories=3,subjects="patient",times=c(1,2,3),corr.mod="uniform",fixed=FALSE,
po.test=TRUE))
```

```
repolr: 2016-02-26 version 3.4

Call:
repolr(formula = activity ~ treat * time, subjects = "patient",
    data = achilles, times = c(1, 2, 3), categories = 3, corr.mod = "uniform",
    po.test = TRUE, fixed = FALSE)

Coefficients:
            coeff    se.robust  z.robust  p.value
cuts1|2     -4.3307   1.2880    -3.3623    0.0008
cuts2|3     -0.8211   1.2571    -0.6532    0.5136
treat        2.0609   1.4079     1.4638    0.1432
time         2.8101   0.7634     3.6810    0.0002
treat:time  -1.7046   0.8265    -2.0624    0.0392

Correlation Structure:  uniform
Estimated Correlation:  0.05
PO Score Test: 2.2943 (d.f. = 3 and p.value = 0.5136)
```

Notice that there is test for 'proportional odds' available with this marginal model called 'PO Score Test'.

This model considers the log of the odds of being below the cut [The regression coefficient estimates then have the reverse sign] Also, the term 'uniform correlation' is the same as 'exchangeable correlation'.

Now another look at the epilepsy study with two marginal models.

```
. xtgee seizures treat vs trv, f(poisson)

GEE population-averaged model                   Number of obs      =       236
Group variable:                    subject      Number of groups   =        59
Link:                                  log      Obs per group: min =         4
Family:                            Poisson                     avg =       4.0
Correlation:                  exchangeable                     max =         4
                                                Wald chi2(3)       =     44.50
Scale parameter:                         1      Prob > chi2        =    0.0000

------------------------------------------------------------------------------
    seizures |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       treat |  -.0003271   .0894684    -0.00   0.997     -.175682    .1750277
          vs |  -.0428057   .0128985    -3.32   0.001    -.0680862   -.0175251
         trv |  -.0314567   .0182241    -1.73   0.084    -.0671753    .0042619
       _cons |   2.257401   .0646655    34.91   0.000     2.130659    2.384143
------------------------------------------------------------------------------


. xtgee seizures treat vs trv, f(nbinomial)

Iteration 1: tolerance = .00011866
Iteration 2: tolerance = 1.531e-08

GEE population-averaged model                   Number of obs      =       236
Group variable:                    subject      Number of groups   =        59
Link:                                  log      Obs per group: min =         4
Family:               negative binomial(k=1)                   avg =       4.0
Correlation:                  exchangeable                     max =         4
                                                Wald chi2(3)       =      5.59
Scale parameter:                         1      Prob > chi2        =    0.1332
```

seizures	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
treat	.0055001	.2868312	0.02	0.985	-.5566786	.5676789
vs	-.0426238	.0387074	-1.10	0.271	-.1184889	.0332413
trv	-.0339837	.0535182	-0.63	0.525	-.1388774	.07091
_cons	2.25697	.2078993	10.86	0.000	1.849495	2.664445