

GEEQBOX: User's Guide

Version 1.0

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Introduction

This document is for help with the use of the MATLAB toolbox **GEEQBOX**. It details how to use the m-files, lists the functions available, and gives a detailed description of each function.

The **GEEQBOX** toolbox can be used to analyze data with correlated outcomes. Version 1.0 of the toolbox currently currently allows for:

- Three possible data distributions.
- Six assumed correlation structures.
- Estimation by either generalised estimating equations (GEE) or quasi-least squares (QLS).

The toolbox, documentation and updates are available from the website:

<http://www.cceb.upenn.edu/~sratclif/QLSproject.html>

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Statistical Background

This GEEQBOX toolbox is for use with correlated data. The most common use is in longitudinal data analysis, where the outcome is observed on each subject at multiple time points over the course of the study. For simplicity, we used subject to indicate the outcomes that are correlated though the correlated measurements may come from a group membership, etc. The outcome can be discrete or continuous and the data can be analyzed using a form of regression analysis for correlated data. The two methods implemented in this toolbox are generalized estimating equations and quasi-least squares.

Both GEE and QLS are iterative approaches that alternate between

1. updating the estimate of the regression parameter β by solving the GEE estimating equation for β and
2. updating the estimate of the correlation parameter α via moment estimation (GEE) or solving an unbiased estimating equation for α in two stages (QLS).

The method of generalized estimating equations (GEE) (Liang and Zeger, 1986) is extremely popular because it allows for straight-forward analysis of correlated outcomes via a marginal model. That is, the model only depends on the covariates of interest, and it does not require any distributional assumptions about the outcomes. The basic idea of GEE is an extension of a generalized linear model which incorporates the covariance matrix of the outcomes for each subject.

The method of quasi-least squares (QLS) is a two-stage approach in the framework of GEE. Chaganty (1997) described QLS for an equal number of observations per subject (balanced data) while Shults (1996) and Shults and Chaganty (1998) extended stage one for several correlation structures and unbalanced data. However, the stage one QLS estimate of the correlation parameter typically is not consistent, even if the correlation structure is correctly specified. Chaganty and Shults (1999) therefore introduced a second stage of QLS that provides a solution to an unbiased estimating equation for the correlation parameter.

GEEQBOX implements both GEE and QLS because QLS may allow for easier implementation of some complex correlation structures, e.g. the Markov correlation structure that is appropriate for longitudinal

studies with variable temporal spacing of measurements. In addition, QLS can also be considered as an alternative approach should the method of GEE fail to converge, or should GEE yield an estimate of the correlation parameter that corresponds to an estimated correlation matrix that is not positive definite (Shults and Chaganty, 1998). For more discussion of QLS that includes a comparison of stage one of QLS versus stage two and a comparison with other approaches see Sun *et al.* (2006).

2.1 Notation

For analysis of a longitudinal study, we assume that outcome measurements $Y_i = (y_{i1}, \dots, y_{in_i})'$ and associated covariates $x'_{ij} = (x_{ij1}, \dots, x_{ijp})$ were collected on subject i at times $T_i = (t_{i1}, \dots, t_{in_i})'$, for $i = 1, \dots, m$. The data are considered balanced and equally spaced when $n_i = n \forall i$ and $|t_{ij} - t_{ik}| = \gamma \forall i, j, k$, respectively. For analysis of a cross-sectional study, e.g. if one measurement is collected on each of several subjects within multiple clusters, then $Y_i = (y_{i1}, \dots, y_{in_i})'$ represents the n_i measurements that were collected within cluster i .

The expected value and variance of measurement y_{ij} on subject i are assumed to equal $E(y_{ij}) = g^{-1}(x'_{ij}\beta) = u_{ij}$ and $Var(y_{ij}) = \phi h(u_{ij})$, respectively, where ϕ is a known or unknown scale parameter. We also let $U_i(\beta)$ represent the $n_i \times 1$ vector of expected values u_{ij} on subject i . For longitudinal and cross-sectional studies, observations are assumed to be independent if they are measured on different subjects. However, within subjects, they are assumed to be correlated, with a pattern of association that can be described by a *working correlation structure*. The working correlation structure for subject i , denoted by $Corr(Y_i) = R_i(\alpha)$, depends on a correlation parameter α that can be scalar or vector-valued. We will underline correlation parameters of dimension greater than one. The covariance matrix of Y_i is then given by $Cov(Y_i) = \phi A_i^{1/2} R_i(\alpha) A_i^{1/2}$, where $A_i = diag(h(u_{i1}), \dots, h(u_{in_i}))$.

2.2 Working Correlation Structures that Can be Implemented with GEEQBOX

GEEQBOX currently implements the following structures, with plans to implement additional structures that will be made available on the website. The **feasible region** for each structure is defined as the interval on which α will yield a positive definite correlation matrix.

- **The Equicorrelated:** This structure assumes that all pairwise correlations within a cluster are equal, so that $Corr(y_{ij}, y_{ik}) = \alpha$. This structure is plausible for cross-sectional studies, e.g. to describe the pattern of association of weights among litter-mates of baby rats. The feasible region for this structure is $(-1/(n_m - 1), 1)$, where n_m represents the maximum value of n_i over $i = 1, 2, \dots, m$.
- **The first-order autoregressive AR(1):** This structure assumes that the correlation among repeated measurements on a subject depends on their separation in order of measurement, so that

$Corr(y_{ij}, y_{ik}) = \alpha^{j-k}$. This structure is plausible for longitudinal studies in which the collection times of measurements are equally spaced in time, e.g. in a weight loss intervention that measures weights on subjects at baseline and then at three and six months post-baseline. The feasible region for this structure is $(-1, 1)$. However, a negative value for α may be biologically implausible because it may be unreasonable to allow the intra-subject correlations to alternate in sign, e.g. for α^2 and α^3 to be positive and negative, respectively.

- **The Markov correlation structure:** This structure assumes that the correlation among repeated measurements on a subject depends on their timing of measurement, so that $Corr(y_{ij}, y_{ik}) = \alpha^{|t_{ij}-t_{ik}|}$. This structure generalizes the AR(1) structure to allow for unequal spacing of measurements. The feasible region for this structure is $(-1, 1)$. However, as for the AR(1) structure, a negative value for α is typically not biologically plausible. GEEQBOX therefore uses QLS to obtain an estimate of $\alpha \in (0, 1)$. We note that GEEQBOX does not implement the Markov structure for GEE because it is not straightforward to obtain a moment estimate for this structure.
- **The tri-diagonal correlation structure:** This structure assumes that the correlation among measurements on a subject is constant for measurements that are separated by one measurement occasion, so that $Corr(y_{ij}, y_{ik}) = \alpha$ for $|j - k| = 1$ and is zero otherwise. The authors are not aware of many practical applications for this structure, but it was implemented in Liang and Zeger (1986) and in most standard software packages that implement GEE. The feasible region for this structure is $\left(\frac{-1}{2 \sin \frac{\pi(n_m-1)}{2(n_m+1)}}, \frac{1}{2 \sin \frac{\pi(n_m-1)}{2(n_m+1)}} \right)$, where n_m is the maximum value of n_i over $i = 1, 2, \dots, m$; this interval is approximately $(-1/2, 1/2)$ for large n and contains $(-1/2, 1/2)$ for all n .
- **Unstructured:** This structure does not assume any pattern for the intra-subject correlations, so that $Corr(Y_{ij}, Y_{ik}) = \alpha_{jk}$. This structure has been implemented in QLS (Chaganty, 1997; Chaganty and Shults, 1999) but the algorithms are somewhat complex. GEEQBOX therefore implements a moment estimate using GEE.
- **Working Independent:** Another popular structure is the identity matrix. Implementation of this structure is straightforward because β can then be estimated in a non-iterative process. However, several authors have shown that incorrect application of the working independence structure can result in a serious loss in efficiency in estimation of β (e.g. Sutradhar and Das, 2000; Wang and Carey, 2004; Shults *et al.*, 2006)

2.3 GEE Estimates of the Correlation Parameter

For GEE, GEEQBOX implements the following moment estimates that are implemented in PROC GENMOD in SAS.

For the equicorrelated structure, the GEE moment estimate is given by:

$$\hat{\alpha}_{GEE-EQUI} = \frac{\sum_{i=1}^m \sum_{j \neq k} z_{ij} z_{ik}}{(N^* - p) \hat{\phi}_{GEE}}$$

where

$$N^* = \sum_{i=1}^m n_i(n_i - 1),$$

$$\hat{\phi}_{GEE} = \frac{\sum_{i=1}^m \sum_{j=1}^{n_i} z_{ij}^2}{N - p},$$

$N = \sum_{i=1}^m n_i$, z_{ij} is the Pearson residual for subject i at time t_{ij} and p is the dimension of β .

For the AR(1) and tri-diagonal estimates, the GEE moment estimate is:

$$\hat{\alpha}_{GEE-TRI} = \hat{\alpha}_{GEE-AR1} = \frac{\sum_{i=1}^m \sum_{j=2}^{n_i} z_{ij} z_{i,j-1}}{(N^{**} - p) \hat{\phi}_{GEE}}$$

where $N^{**} = \sum_{i=1}^m (n_i - 1)$.

For the unstructured correlation matrix, GEEQBOX implements the following moment estimate for element j, k of the matrix:

$$R_i[j, k] = \frac{\sum_{i=1}^m z_{ij} z_{ik}}{(m - p) \hat{\phi}_{GEE}}$$

A moment based estimator has not been proposed in the literature for implementation of the more general Markov correlation for GEE, which provides motivation for implementation of QLS.

2.4 QLS Estimates of the Correlation Parameter

While GEE typically uses moment estimates for α , QLS estimates α by obtaining a solution to an unbiased estimating equation in two stages (see Sun *et al.*, 2006, for more details). In stage one, QLS alternates between updating the estimates of β and solving the *stage one estimating equation* for α until convergence.

$$\frac{\partial}{\partial \alpha} \left\{ \sum_{i=1}^m Z'_i(\beta) \{R_i^{-1}(\alpha)\} Z_i(\beta) \right\} = 0 \quad (2.1)$$

where $Z_i(\beta) = (z_{i1}, z_{i2}, \dots, z_{in_i})_{n_i \times 1}$ is the vector of Pearson residuals on subject i .

The solution $\hat{\alpha}$ to (2.1) is not consistent. Stage two of QLS therefore obtains a consistent estimate $\hat{\alpha}_{QLS}$ as the solution to the *stage two estimating equation* for α .

$$\sum_{i=1}^m \text{trace} \left\{ \frac{\partial R_i^{-1}(\delta)}{\partial \delta} R_i(\alpha) \right\} \bigg|_{\delta=\hat{\alpha}} = 0 \quad (2.2)$$

The final QLS estimate $\hat{\beta}_{QLS}$ of β is then obtained by solving the GEE estimating equation for β evaluated at $\hat{\alpha}_{QLS}$. For estimating equations that do not have a unique solution, GEEQBOX uses the bisection method to obtain a solution in the feasible region for α .

For the AR(1) structure and for unbalanced data, Shults and Chaganty (1998) proved that the feasible stage one estimate $\hat{\alpha}$ can be expressed as:

$$\hat{\alpha}_{QONE} = \frac{\sum_{i=1}^m \sum_{j=2}^{n_i} (z_{ij}^2 + z_{ij-1}^2) - \sqrt{\sum_{i=1}^m \sum_{j=2}^{n_i} (z_{ij}^2 + z_{ij-1}^2) \sum_{i=1}^m \sum_{j=2}^{n_i} (z_{ij}^2 - z_{ij-1}^2)}}{2 \sum_{i=1}^m \sum_{j=2}^{n_i} z_{ij} z_{ij-1}} \quad (2.3)$$

while the stage two estimate $\hat{\alpha}_{QLS-AR1}$ (Chaganty and Shults, 1999) is given by

$$\hat{\alpha}_{QLS-AR1} = \frac{2\hat{\alpha}_{QONE}}{1 + \hat{\alpha}_{QONE}^2}. \quad (2.4)$$

For the Markov structure and unbalanced data, Shults and Chaganty (1998) provided the QLS stage one estimating equation for α :

$$\sum_{i=1}^m \sum_{j=2}^{n_i} \frac{e_{ij} \alpha^{e_{ij}} \left[\alpha^{2e_{ij}} z_{ij} z_{i,j-1} - \alpha^{e_{ij}} (z_{ij}^2 + z_{i,j-1}^2) + z_{ij} z_{i,j-1} \right]}{1 - \alpha^{2e_{ij}}} = 0 \quad (2.5)$$

where $e_{ij} = |t_{ij} - t_{i,j-1}|$. Note that GEEQBOX requires that $e_{ij} \geq 1 \forall i$ and j . The stage two estimating equation for the Markov structure (Chaganty and Shults, 1999) is given by:

$$\sum_{i=1}^m \sum_{j=2}^{n_i} \frac{2e_{ij} \delta^{2e_{ij}-1} - \alpha^{e_{ij}} e_{ij} [\delta^{e_{ij}-1} + \delta^{3e_{ij}-1}]}{1 - \delta^{2e_{ij}}} \Bigg|_{\delta=\hat{\alpha}} = 0 \quad (2.6)$$

For the equicorrelated structure and for unbalanced data, Shults and Chaganty (1998) proved that there will be a unique feasible solution to the following stage one estimating equation for α :

$$\sum_{i:n_i>1} Z_i' Z_i - \sum_{i:n_i>1} \frac{1 + \alpha^2(n_i - 1)}{(1 + \alpha(n_i - 1))^2} (Z_i'(\beta) e_i)^2 = 0 \quad (2.7)$$

where I_{n_i} is the identity matrix and e_i is a $n_i \times 1$ column vector of ones. Shults and Morrow (2002) obtained the stage two estimate $\hat{\alpha}_{QLS-EQC}$:

$$\sum_{i:n_i>1} \frac{n_i (n_i - 1) \hat{\alpha} (\hat{\alpha} (n_i - 2) + 2)}{(1 + \hat{\alpha}(n_i - 1))^2} / \sum_{i:n_i>1} \frac{n_i (n_i - 1) (1 + \hat{\alpha}^2(n_i - 1))}{(1 + \hat{\alpha}(n_i - 1))^2} \quad (2.8)$$

For the tri-diagonal structure and unbalanced data, GEEQBOX obtains solutions to the stage one and two estimating equations (2.1) and (2.2) for the tri-diagonal structure by first constructing the tri-diagonal matrix $R_i(\hat{\alpha})$. Next, to evaluate

$$\frac{\partial R_i^{-1}(\delta)}{\partial \delta} \Bigg|_{\delta=\hat{\alpha}}$$

GEEQBOX implements the following expression:

$$\frac{\partial R_i^{-1}(\delta)}{\partial \delta} \Bigg|_{\delta=\hat{\alpha}} = -R_i^{-1}(\hat{\alpha}) \frac{\partial R_i(\delta)}{\partial \delta} \Bigg|_{\delta=\hat{\alpha}} R_i^{-1}(\hat{\alpha})$$

where $\frac{\partial R_i(\delta)}{\partial \delta}$ is an $n_i \times n_i$ matrix with ones on the off-diagonal and zero elsewhere, i.e. the $(j, k)^{th}$ element of $\frac{\partial R_i(\delta)}{\partial \delta}$ is 1 if $|j - k| = 1$ and is 0 otherwise.

2.5 Confidence Intervals and P-values for Tests of Hypotheses Involving the Regression Parameter

The asymptotic distribution of the QLS estimate $\hat{\beta}_{QLS}$ is the same as the asymptotic distribution of the GEE estimate $\hat{\beta}_{GEE}$. GEEQBOX therefore provides both model based and sandwich-based estimates of the covariance matrix of $\hat{\beta}$ (Liang and Zeger, 1986). The covariance matrix depends on the scalar parameter ϕ ; GEEQBOX implements the estimate provided in Chaganty and Shults (1999). The *model based* estimate of the covariance matrix is appropriate when the user has a high degree of confidence that the correlation structure has been correctly specified. It has the following form:

$$\widehat{Cov}_M(\hat{\beta}) = \hat{\phi} W_m^{-1},$$

where

$$W_m = \sum_{i=1}^m X_i' A_i^{1/2} R_i^{-1}(\hat{\alpha}) A_i^{1/2} X_i$$

and $\hat{\phi} = \min \{ \hat{\phi}_p, \hat{\phi}_c \}$, for

$$\hat{\phi}_p = \frac{1}{m} \sum_{i=1}^m \frac{Z_i(\hat{\beta})' Z_i(\hat{\beta})}{n_i} \text{ and } \hat{\phi}_c = \frac{1}{m} \sum_{i=1}^m \frac{Z_i(\hat{\beta})' R_i^{-1}(\hat{\alpha}) Z_i(\hat{\beta})}{n_i}.$$

The *robust sandwich* covariance matrix has the following form:

$$\widehat{Cov}_R(\hat{\beta}) = W_m^{-1} \left\{ \sum_{i=1}^m X_i' A_i^{1/2} R_i^{-1}(\hat{\alpha}) Z_i(\hat{\beta}) Z_i'(\hat{\beta}) R_i^{-1}(\hat{\alpha}) A_i^{1/2} X_i \right\} W_m^{-1}. \quad (2.9)$$

GEEQBOX provides estimated standard errors, 95% confidence intervals, and p -values for the tests $\beta_j = 0$ that are based on both the *model* and *sandwich* covariance matrices.

3

Performing Analyses

There are two main functions, `gee` and `qls`, that can be used to analyze the correlated data. These functions take the same inputs and produce the same outputs. This chapter explains how the data must be set-up for analysis, what results are obtained and give an example of their use.

3.1 Data Set-up

Before using one of the analysis functions, the data must be organized such that each outcome measurement (Y) and associated id's, time points (t), and covariates (X) are listed on a separate row. That is,

$$Y = \begin{bmatrix} y_{11} \\ y_{12} \\ \vdots \\ y_{1n_1} \\ y_{21} \\ \vdots \\ y_{2n_2} \\ \vdots \\ y_{n1} \\ \vdots \\ y_{nn_n} \end{bmatrix} \quad \text{id} = \begin{bmatrix} 1 \\ 1 \\ \vdots \\ 1 \\ 2 \\ \vdots \\ 2 \\ \vdots \\ n \\ \vdots \\ n \end{bmatrix} \quad t = \begin{bmatrix} t_{11} \\ t_{12} \\ \vdots \\ t_{1n_1} \\ t_{21} \\ \vdots \\ t_{2n_2} \\ \vdots \\ t_{n1} \\ \vdots \\ t_{nn_n} \end{bmatrix} \quad X = \begin{bmatrix} x_{11} \\ x_{12} \\ \vdots \\ x_{1n_1} \\ x_{21} \\ \vdots \\ x_{2n_2} \\ \vdots \\ x_{n1} \\ \vdots \\ x_{nn_n} \end{bmatrix}$$

$$i = 1, \dots, n, \quad j = 1, \dots, n_i$$

where y_{ij} is the j -th measurement on the i -th subject, t_{ij} is the associated time point and x_{ij} is the row vector of covariates at time t_{ij} .

In addition, as shown above, the measurements must be sorted so that all measurements from the same subject (id) are listed on consecutive rows. If the id vector consisted of $[1\ 1\ 2\ 2\ 2\ 1\ 1]^T$, then the program would count this as 3 subjects since there are 3 changes in id numbers. However, the id's do not have to be consecutive numbers. For example, $\text{id}=[12\ 12\ 12\ 10\ 10\ 10\ 99\ 99]^T$ would produce the same results as $\text{id}=[1\ 1\ 1\ 2\ 2\ 2\ 3]^T$.

The matrix of covariates, X , should be set-up so that each column contains a separate covariate. At present, there should be no missing data in X . A constant term is not included by default in the programs. Thus, in order to include a constant in the model, a column of ones must be included as a covariate in X . This column of ones should be the *final* column of X . The programs will default to calling the beta estimate by the associated column number of X . However, this can be over-written with the optional **varnames** input. Varnames should be a cell row array that defines the names to be used instead of 1, 2, etc. For example, if X contains the covariates, in order, time, age and a constant term, then varnames could be defined as `varnames={'time','age','constant'}`.

3.2 Results

Each function produces the same printed results and output variables. The printed results consist of the initial values used by the algorithms, the estimated covariance parameter (α), scale parameter (ϕ), and the covariate parameter estimates (β). In addition, the standard errors, corresponding z-values, p-values and 95% confidence intervals for each β_j are also given. Two versions of these values are presented; the one based on the robust covariance matrix and the one based on the model based covariance matrix. The model based results should be used when the specified working correlation matrix is known to be correct; otherwise, the robust results should be used.

Three variables are produced as outputs to the functions. These are the estimated β 's, α , and a structured variable results that contains the entire printed results from the robust estimations in the cell variable `results.robust` and the model based estimation in the cell variable `results.model`.

3.3 Example

We use the data provided in Table 3 of Nunez-Anton and Woodworth (1994) of illustrate the use of the functions. This data is contained in the files `audio.dat` (ascii file) and `audio.mat` (Matlab data file), which can be obtained from the web site.

The data consists of the following variables: subject id; group (=0 for A; =1 for B); month of measurement; percent; and high (=0 for percent<50; =1 for percent \geq 50). The variable percent represents the "percent correct scores on a sentence test administered under audition-only conditions to groups of subjects wearing two different cochlear implants, referred to here as A and B. The electrode array was surgically implanted 5 to 6 weeks prior to being electrically connected to the external speech processor.

Subjects were profoundly, bilaterally deaf, thus preconnection baseline values for the sentence test were all zero. At the time of the analysis reported here, data were available for 23 subjects in group A and 21 subjects in group B, with measurements scheduled at 1, 9, 18, 30 months after connection.” (Nunez-Anton and Woodworth, 1994)

```
>> load('audio.dat');
>> id = audio(:,1);
>> group = audio(:,2);
>> month = audio(:,3);
>> percent = audio(:,4);
>> high = audio(:,5);
>> cons = ones(136,1);
```

In the worked examples presented here $\beta = (\beta_1, \beta_2, \beta_3)$ where β_1 is the regression coefficient associated with month of measurement; β_2 is the regression coefficient associated with group (group = 0 for A; group = 1 for B); and β_3 is the regression coefficient associated with cons, the constant that takes value one. There are two outcomes to be considered: the continuous outcome percent, and the binary outcome high. Thus, the X matrix of interest is set as

```
>> X=[month group cons];
```

and the associated variable names for displaying the results are

```
>> varnames={'month','group','cons'};
```

For the continuous outcome percent, we first estimate the parameters using QLS and assuming a normal distribution for Y (identity link) and an Markov correlation structure. The distribution/link can be set using the 5th input (Family), and the working correlation structure using the 6th input (CorrStruct). The normal distribution is set using the option 'n', while the Markov assumption is specified via 'markov'. These inputs are not case sensitive; thus 'N', 'Markov', 'MARKOV', etc. would all have be acceptable. Thus, the command to perform the analysis, and resulting output, would be:

```
>>[betahat,alphahat,results] = qls(id,percent,month,X,'n','markov',varnames);
```

Normal distribution family assumed

Markov Correlation structure assumed

Initial estimate of beta = [0.830658 -9.50759 28.2862]

Stage 1 estimate of alpha = 0.94555

Stage 1 estimate of beta = [0.966584 -10.8228 26.2529]

Stage 2 estimate of alpha = 0.98623

Stage 2 estimate of beta = [1.05273 -12.0745 25.3058]

QLS estimate of scale parameter = 720.8796

Estimates based on ROBUST covariance matrix

Columns 1 through 5

'Variable'	'Beta'	'Std.Error'	'z value'	'p-value'
'month'	[1.0527]	[0.1399]	[7.5231]	[5.3513e-014]
'group'	[-12.0745]	[7.3972]	[-1.6323]	[0.1026]
'constant'	[25.3058]	[5.1899]	[4.8760]	[1.0827e-006]

Columns 6 through 7

'95% CI'	
'low lim'	'up lim'
[0.7785]	[1.3270]
[-26.5727]	[2.4237]
[15.1338]	[35.4778]

Estimates based on MODEL based covariance matrix

Columns 1 through 5

'Variable'	'Beta'	'Std.Error'	'z value'	'p-value'
'month'	[1.0527]	[0.1388]	[7.5848]	[3.3307e-014]
'group'	[-12.0745]	[7.6073]	[-1.5872]	[0.1125]
'constant'	[25.3058]	[5.5109]	[4.5919]	[4.3917e-006]

Columns 6 through 7

'95% CI'	
'low lim'	'up lim'
[0.7807]	[1.3248]
[-26.9845]	[2.8355]
[14.5046]	[36.1070]

Similarly, using GEEs and assuming an equicorrelated covariance structure, we would obtain:

```
>> [betahat,alphaht,results] = gee(id,percent,month,X,'n','equi',varnames);
Normal distribution family assumed
Equicorrelated structure assumed
```

GEE estimate of alpha = 0.89733

GEE estimate of beta = [0.909073 -11.9411 28.4943]

GEE estimate of scale parameter = 718.7803

Estimates based on ROBUST covariance matrix

Columns 1 through 5

	''	''	''	''	''
'Variable'	'Beta'	'Std.Error'	'z value'	'p-value'	
'month'	[0.9091]	[0.1288]	[7.0602]	[1.6627e-012]	
'group'	[-11.9411]	[7.5661]	[-1.5782]	[0.1145]	
'constant'	[28.4943]	[5.3765]	[5.2998]	[1.1596e-007]	

Columns 6 through 7

'95% CI'	''
'low lim'	'up lim'
[0.6567]	[1.1614]
[-26.7705]	[2.8883]
[17.9565]	[39.0322]

Estimates based on MODEL based covariance matrix

Columns 1 through 5

	''	''	''	''	''
'Variable'	'Beta'	'Std.Error'	'z value'	'p-value'	
'month'	[0.9091]	[0.0825]	[11.0201]	[0]	
'group'	[-11.9411]	[7.8167]	[-1.5276]	[0.1266]	
'constant'	[28.4943]	[5.4790]	[5.2007]	[1.9859e-007]	

Columns 6 through 7

'95% CI'	''
'low lim'	'up lim'
[0.7474]	[1.0708]
[-27.2616]	[3.3794]
[17.7557]	[39.2330]

To model the binary outcome high, we need to use the Bernoulli distribution assumption. This is done by setting the 'Family' input to 'b'. The QLS estimates under a tr-diagonal correlation assumption are

shown below.

```
>> [betahat,alphahat,results] = qls(id,high,month,X,'b','tri',varnames);
```

Bernoulli distribution family assumed

Tri-diagonal Correlation structure assumed

Initial estimate of beta = [0.049843 -0.81037 -1.0891]

Stage 1 estimate of alpha = 0.31269

Stage 1 estimate of beta = [0.053484 -0.79452 -1.1604]

Stage 2 estimate of alpha = 0.51664

Stage 2 estimate of beta = [0.056485 -0.76032 -1.2516]

QLS estimate of scale parameter = 1

Estimates based on ROBUST covariance matrix

Columns 1 through 5

	''	''	''	''	''
'Variable'	'Beta'	'Std.Error'	'z value'	'p-value'	
'month'	[0.0565]	[0.0183]	[3.0923]	[0.0020]	
'group'	[-0.7603]	[0.6172]	[-1.2318]	[0.2180]	
'constant'	[-1.2516]	[0.4182]	[-2.9928]	[0.0028]	

Columns 6 through 7

'95% CI'	''
'low lim'	'up lim'
[0.0207]	[0.0923]
[-1.9701]	[0.4494]
[-2.0712]	[-0.4319]

Estimates based on MODEL based covariance matrix

Columns 1 through 5

	''	''	''	''	''
'Variable'	'Beta'	'Std.Error'	'z value'	'p-value'	
'month'	[0.0565]	[0.0193]	[2.9196]	[0.0035]	
'group'	[-0.7603]	[0.5018]	[-1.5151]	[0.1297]	
'constant'	[-1.2516]	[0.4133]	[-3.0283]	[0.0025]	

Columns 6 through 7

'95% CI'	''
'low lim'	'up lim'
[0.0186]	[0.0944]
[-1.7439]	[0.2233]
[-2.0616]	[-0.4415]

4

Functions

The detailed description for each function is organized as follows:

- name of function
- a statement of purpose
- a synopsis of the function's syntax
- a description of what the function does

and, for selected functions,

- examples
- a detailed description of the mathematical procedure/equations comprising the function.

4.1 Reference Tables

The GEEQBOX toolbox contains the following functions:

Top Level Function	
<code>qls</code>	Analyzes correlated data via QLS.
<code>gee</code>	Analyzes correlated data via GEEs.

Called Functions (sub-routines)	
<code>counti</code>	Counts the number of times each unique element occurs in a vector.
<code>fequi1</code>	Computes the stage 1 QLS estimates for the equicorrelated structure assumption.
<code>fmark1</code>	Computes the stage 1 QLS estimates for the Markov correlation structure assumption.
<code>fmark2</code>	Computes the stage 2 QLS estimates for the Markov correlation structure assumption.
<code>ftri1</code>	Computes the stage 1 QLS estimates for the tri-diagonal correlation structure assumption.
<code>ftri2</code>	Computes the stage 2 QLS estimates for the tri-diagonal correlation structure assumption.
<code>ftri2a</code>	Computes the stage 2 QLS estimates for the tri-diagonal correlation structure assumption.

4.2 Commands and Functions

counti

Purpose	Counts the number of times each unique element occurs in a vector
Syntax	<code>[ni,n] = counti(x);</code>
Description	<code>[ni,n] = counti(x)</code> for a vector of non-unique elements, <code>x</code> , returns the number of times each unique element is contained in <code>x</code> in <code>ni</code> . The number of unique elements is optionally returned in <code>n</code> . Note: the non-unique elements of <code>x</code> must be grouped together and <code>ni</code> will contain the number of each non-unique element in the order in which they appear in <code>x</code> .

fequi1

Purpose	Computes the stage 1 QLS estimates for the equicorrelated structure assumption.
Syntax	<code>fa = fequi1(x,p1,p2,p3);</code>
Description	<code>fa = fequi1(x,p1,p2,p3);</code> is used to find the optimize <code>x</code> in the stage 1 QLS function assuming an equicorrelated structure and given known parameters <code>p1</code> , <code>p2</code> , and <code>p3</code> . That is, it is called by <code>qls</code> when the equicorrelated option has been specified.

fmark1

Purpose	Computes the stage 1 QLS estimates for the Markov correlation structure assumption.
Syntax	<code>fa = fmark1(x,p1,p2,p3,p4);</code>
Description	<code>fa = fmark1(x,p1,p2,p3,p4);</code> is used to find the optimize <code>x</code> in the stage 1 QLS function assuming a Markov correlation structure and given known parameters <code>p1</code> , to <code>p4</code> . That is, it is called by <code>qls</code> when the Markov option has been specified.
See Also	<code>fmark2</code>

fmark2

Purpose	Computes the stage 2 QLS estimates for the Markov correlation structure assumption.
----------------	---

Syntax	<code>fa = fmark2(x,p1,p2);</code>
Description	<code>fa = fmark1(x,p1,p2);</code> is used to find the optimize <code>x</code> in the stage 2 QLS function assuming a Markov correlation structure and given known parameters <code>p1</code> , and <code>p2</code> . That is, it is called by <code>qls</code> when the Markov option has been specified.
See Also	<code>fmark1</code>

ftri1

Purpose	Computes the stage 1 QLS estimates for the Tri-diagonal correlation structure assumption.
Syntax	<code>fa = ftri1(x,p1,p2,p3,p4);</code>
Description	<code>fa = ftri1(x,p1,p2,p3,p4);</code> is used to find the optimize <code>x</code> in the stage 1 QLS function assuming a tri-diagonal correlation structure and given known parameters <code>p1</code> , to <code>p4</code> . That is, it is called by <code>qls</code> when the Tri-diagonal option has been specified.
See Also	<code>ftri2</code> <code>ftri2a</code>

ftri2

Purpose	Computes the stage 2 QLS estimates for the Tri-diagonal correlation structure assumption.
Syntax	<code>fa = ftri2(x,p1,p2,p3,p4,p5);</code>
Description	<code>fa = ftri2(x,p1,p2,p3,p4,p5);</code> is used to find the optimize <code>x</code> in the stage 2 QLS function assuming a tri-diagonal correlation structure and given known parameters <code>p1</code> , to <code>p5</code> . That is, it is called by <code>qls</code> when the Tri-diagonal option has been specified. It is called when an absolute zero exists within the feasible region for the estimate.
See Also	<code>ftri1</code> <code>ftri2a</code>

ftri2a

Purpose	Computes the stage 2 QLS estimates for the Tri-diagonal correlation structure assumption.
Syntax	<code>fa = ftri2a(x,p1,p2,p3,p4,p5);</code>

Description `fa = ftri2a(x,p1,p2,p3,p4,p5);` is used to find the optimize `x` in the stage 2 QLS function assuming a tri-diagonal correlation structure and given known parameters `p1`, to `p5`. That is, it is called by `qls` when the Tri-diagonal option has been specified. It is called when an absolute zero does not exist within the feasible region for the estimate. Instead, it finds the value of `x` closest to zero within the feasible region.

See Also `ftri1 ftri2a`

gee

Purpose Analyses correlated data via GEE.

Syntax

```
[bhat,alpha,results] = gee(id,y,t,X);
[bhat,alpha,results] = gee(id,y,t,X,Family);
[bhat,alpha,results] = gee(id,y,t,X,Family,CorrStruct);
[bhat,alpha,results] = gee(id,y,t,X,Family,CorrStruct,varnames);
[bhat,alpha,results] = gee(id,y,t,X,Family,CorrStruct,varnames,tol);
[bhat,alpha,results] = gee(id,y,t,X,Family,CorrStruct,varnames,tol,maxit);
```

Description `[bhat,alpha,results] = gee(id,y,t,X);` analyses correlated data via GEEs where `y` is a $N \times 1$ vector containing the repeated measures data, measured at corresponding times `t`, on subjects `id`, regressed on fixed covariates `X`. In order for a constant to be included in the model, the final column of `X` could be a column of ones. For all these variables, the number of rows should be equal to

$$N = \sum_{i=1}^n n_i$$

This model assumes the data follows a normal distribution with a Markov correlation structure. `[bhat,alpha,results] = gee(id,y,t,X,Family,CorrStruct);` can be used to change these assumptions. `Family` specifies the assumed distribution of the data. It can take values:

- 1 or `n` for a Normal distribution (default);
- 2 or `b` for a Bernoulli distribution; or
- 3 or `p` for a Poisson distribution.

`CorrStruct` specifies the assumed correlation structure. It can take values:

- 1 or `ar1` for an AR(1) structure;
- 2 or `markov` for a Markov structure (default);
- 3 or `equi` for an Equicorrelated structure;
- 4 or `tri` for a Tri-diagonal correlation structure;
- 5 or `un` for an Unstructured correlation matrix; or
- 6 or `ind` for a working Independent correlation structure.

Further, `varnames` can be used to specify the variables names to be used in the output.

This is a cell row array which corresponds to the variables entered in **X**. Additionally, **maxit** specifies the maximum number of iterations (default is 100), and **tol** the tolerance used for determining convergence (default is 1e-5).

[bhat,alpha,results] contains the parameter estimates for the fixed effects **X** in **bhat**, and the estimated correlation parameters in **alpha**. **results** is a structured array with two elements, **robust** and **model** which contains the entire printed results / estimates under the robust and model based covariance matrices, respectively.

Examples To fit the regression model

$$Y_i = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \varepsilon_i$$

where **id** and **time** contains the *i*'s and time points associated with each row. Under a normal distribution and Markov working correlation structure, the model would be fit with the commands

```
X = [X1,X2,ones(length(Y,1))];
varnames = {'X1','X2','constant'};
[bhat,alpha,results] = gee(id,Y,time,X,'n','markov',varnames);
```

The results from fitting this model to some data would be:

```
Normal distribution family assumed
AR(1) Correlation structure assumed
```

```
GEE estimate of alpha = 0.85796
GEE estimate of beta = [0.67155 -0.0037861      0.8628]
```

```
GEE estimate of scale parameter = 0.61616
```

```
Estimates based on ROBUST covariance matrix
Columns 1 through 5
```

	''	''	''	''	''
'Variable'	'Beta'	'Std.Error'	'z value'	'p-value'	
[1]	[0.6715]	[0.0572]	[11.7442]	[0]	
[2]	[-0.0038]	[0.0024]	[-1.5532]	[0.1204]	
[3]	[0.8628]	[0.0586]	[14.7258]	[0]	

```
Columns 6 through 7
```

'95% CI'	''
'low lim'	'up lim'
[0.5595]	[0.7836]
[-0.0086]	[9.9147e-004]

[0.7480] [0.9776]

Estimates based on MODEL based covariance matrix
Columns 1 through 5

,,		,,		,,		,,		,,	
'Variable'		'Beta'		'Std.Error'		'z value'		'p-value'	
[1]		[0.6715]		[0.0510]		[13.1793]		[0]	
[2]		[-0.0038]		[0.0018]		[-2.0659]		[0.0388]	
[3]		[0.8628]		[0.0747]		[11.5564]		[0]	

Columns 6 through 7

'95% CI'		,,	
'low lim'		'up lim'	
[0.5717]		[0.7714]	
[-0.0074]		[-1.9423e-004]	
[0.7165]		[1.0091]	

qls

Purpose	Analyses correlated data via QLS.
Syntax	<code>[bhat,alpha,results]=qls(id,y,t,X);</code> <code>[bhat,alpha,results] = qls(id,y,t,X,Family);</code> <code>[bhat,alpha,results] = qls(id,y,t,X,Family,CorrStruct);</code> <code>[bhat,alpha,results] = qls(id,y,t,X,Family,CorrStruct,varnames);</code> <code>[bhat,alpha,results] = qls(id,y,t,X,Family,CorrStruct,varnames,tol);</code> <code>[bhat,alpha,results] = qls(id,y,t,X,Family,CorrStruct,varnames,tol,maxit);</code>
Description	<code>[bhat,alpha,results] = qls(id,y,t,X);</code> analyses correlated data via QLS where y is a $N \times 1$ vector containing the repeated measures data, measured at corresponding times t, on subjects id, regressed on fixed covariates X. In order for a constant to be included in the model, the final column of X could be a column of ones. For all these variables, the number of rows should be equal to

$$N = \sum_{i=1}^n n_i$$

This model assumes the data follows a normal distribution with a Markov correlation structure. `[bhat,alpha,results] = qls(id,y,t,X,Family,CorrStruct);` can be used to change these assumptions. `Family` specifies the assumed distribution of the data.

It can take values:

- 1 or **n** for a Normal distribution (default);
- 2 or **b** for a Bernoulli distribution; or
- 3 or **p** for a Poisson distribution.

CorrStruct specifies the assumed correlation structure. It can take values:

- 1 or **ar1** for an AR(1) structure;
- 2 or **markov** for a Markov structure (default);
- 3 or **equi** for an Equicorrelated structure;
- 4 or **tri** for a Tri-diagonal correlation structure;
- 5 or **un** for an Unstructured correlation matrix; or
- 6 or **ind** for a working Independent correlation structure.

Further, **varnames** can be used to specify the variables names to be used in the output. This is a cell row array which corresponds to the variables entered in **X**. Additionally, **maxit** specifies the maximum number of iterations (default is 100), and **tol** the tolerance used for determining convergence (default is 1e-5).

[bhat,alpha,results] contains the parameter estimates for the fixed effects **X** in **bhat**, and the estimated correlation parameters in **alpha**. **results** is a structured array with two elements, **robust** and **model** which contains the entire printed results / estimates under the robust and model based covariance matrices, respectively.

Examples

To fit the regression model

$$Y_i = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \varepsilon_i$$

where **id** and **time** contains the *i*'s and time points associated with each row. Under a normal distribution and Markov working correlation structure, the model would be fit with the commands

```
X = [X1,X2,ones(length(Y,1))];
varnames = {'X1','X2','constant'};
[bhat,alpha,results] = qls(id,Y,time,X,'n','markov',varnames);
```

The results from fitting this model to some data would be:

```
Normal distribution family assumed
Markov Correlation structure assumed
Initial estimate of beta = [0.62771    -0.002418    0.97107]

Stage 1 estimate of alpha = 0.88122
Stage 1 estimate of beta = [0.61824 -0.00027181    0.87907]

Stage 2 estimate of alpha = 0.96007
Stage 2 estimate of beta = [0.63961    0.0014781    0.78748]
```


QLS estimate of scale parameter = 0.60842

Estimates based on ROBUST covariance matrix

Columns 1 through 5

	''	''	''	''	''
'Variable'	'Beta'	'Std.Error'	'z value'	'p-value'	
'X1'	[0.6396]	[0.0667]	[9.5896]	[0]	
'X2'	[0.0015]	[0.0030]	[0.4916]	[0.6230]	
'Constant'	[0.7875]	[0.0613]	[12.8423]	[0]	

Columns 6 through 7

'95% CI'	''
'low lim'	'up lim'
[0.5089]	[0.7703]
[-0.0044]	[0.0074]
[0.6673]	[0.9077]

Estimates based on MODEL based covariance matrix

Columns 1 through 5

	''	''	''	''	''
'Variable'	'Beta'	'Std.Error'	'z value'	'p-value'	
'X1'	[0.6396]	[0.0457]	[13.9809]	[0]	
'X1'	[0.0015]	[0.0022]	[0.6773]	[0.4982]	
'Constant'	[0.7875]	[0.0758]	[10.3936]	[0]	

Columns 6 through 7

'95% CI'	''
'low lim'	'up lim'
[0.5499]	[0.7293]
[-0.0028]	[0.0058]
[0.6390]	[0.9360]

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