Lecture 13—Tuesday, February 23, 2010

Outline of lecture

Correlated data analysis III: Generalized estimating equations (GEE)

So far we've discussed generalized least squares and mixed effects models as methods for handling correlated data. A third approach to correlated data analysis is generalized estimating equations or GEE. GEE is to generalized linear models (GLM) as GLS is to ordinary least squares (OLS). Just like GLS, GEE can incorporate a correlation matrix of the response variable when estimating parameters. With hierarchical data sets GEE yields what's called a marginal regression model. To understand the ramifications of this we first need to review the concept of a link function and discuss how a link function differs from variable transformation.

Variable transformations versus link functions

Let Y be a positive, continuous response variable. For instance Y might denote biological size measured over time. If the full range of an organism's life span is under consideration some values of Y will be near zero (occurring early in the organism's life span), and others will be far removed from zero (occurring later in the life span). Suppose we fit an ordinary regression model in which we assume that the ith individual's mean size varies linearly on the jth occasion with a time-dependent predictor x_{ij} (such as its age) and perhaps other predictors.

$$Y_{ij} \sim \text{Normal}\left(\mu_{Y_{ij}}, \sigma^2\right)$$
$$\mu_{Y_{ij}} = \beta_0 + \beta_1 x_{ij} + \cdots$$

This is probably a silly model. Because the normal distribution is an unbounded distribution, it allows Y to take negative values. The probability that Y is negative could be non-negligible for small predicted values of the mean. The presence of a lower bound of zero will also restrict the variability of the response. If Y is predicted to be close to the boundary for some values of x, its overall distribution will tend to be heteroscedastic as a function of x. Because the normal distribution for Y assumes the variance is constant and independent of the mean, heteroscedasticity indicates yet another problem with a normal model for these data.

Transforming the response variable

The classical approach to handling this problem would be to transform the response and assume that the transformed variable has a normal distribution with constant variance. For the scenario I've described a common choice would be a log transformation. Thus we would assume

$$\log Y_{ij} \sim \text{Normal}\left(\mu_{\log Y_{ij}}, \sigma^2\right)$$
$$\mu_{\log Y_{ij}} = \beta_0 + \beta_1 x_{ij} + \cdots$$

The notation used in the regression equation is meant to indicate that we are modeling the mean of log Y rather than mean of Y. In the first regression model the regression equation yields the mean of the response on the original raw scale of the response. In the transformed regression model the regression equation yields the mean of the response on a log scale. These are obviously not the same. Furthermore there is no way to transform a mean on the log scale into a mean on the raw scale.

Although exponentiating the regression equation for log Y does yield a value that is on the scale of the raw response, it does not yield the mean of the response on the raw scale. The problem mathematically is that the "mean function" and the exponential function don't commute and so the exponential and logarithm operations can't cancel each other out.

$$\exp\left[\mu(\log Y)\right] \neq \mu\left[\exp(\log Y)\right] = \mu(Y)$$

On the other hand, because

1. the mean and median of a normal distribution are the same, and
2. the logarithm is a monotonic transformation,

exponentiating the regression equation for mean log Y does yield an expression for the median response on the raw scale (but not the mean).

Choosing a probability distribution and a link function

The modern approach to handling data of this sort is to choose a probability distribution that is more appropriate for a positive, continuous response variable. (In reality this is not really so different from the classical approach. Log-transforming a response and assuming the log is normally distributed is equivalent to assuming that the original response variable has a lognormal distribution. The lognormal distribution is a probability distribution that is appropriate for a positive, continuous response variable.) In the generalized linear model framework a reasonable

choice for the probability distribution would be a gamma distribution.

$$Y \sim \text{Gamma}(a, b)$$

where $a > 0$ and $b > 0$. The parameters a and b are related to the mean and variance of the gamma distribution as follows.

$$\mu = \frac{a}{b}, \ \sigma^2 = \frac{a}{b^2} = \frac{1}{b}\mu = \frac{1}{a}\mu^2$$

Because a and b are positive, the mean of the gamma distribution is positive. To guarantee that the regression equation only returns positive values for the mean, the usual approach is to formulate a regression equation for log μ rather than μ. The log function used in this way is referred to as a link function because it links the mean of a gamma distribution to the linear predictor of the regression model.

$$Y_{ij} \sim \text{Gamma}(a_{ij}, b_{ij})$$
$$\log \mu_{Y_{ij}} = \beta_0 + \beta_1 x_{ij} + \cdots$$

Typically one of a or b, usually b, is treated as a constant.

Unlike the case of a log-transformed regression model, when a log link is used it is possible to recover the mean on the raw scale by exponentiating both sides of the regression equation.

$$\exp\left[\log(\mu(Y))\right] = \mu(Y)$$

So, by choosing a log link function and a gamma distribution for positive data we do end up with a model for the mean on the raw scale. This makes using a generalized linear model an attractive alternative to transforming the response variable.

One possible drawback with both a log transformed response and the use of a log link function is that in the end our predictors have multiplicative effects rather than additive ones on the scale of the original response.

$$\left.\begin{array}{ll}\text{lognormal:} & \exp\left[\mu\left(\log Y_{ij}\right)\right] \\ \text{gamma:} & \mu\left(Y_{ij}\right)\end{array}\right\} = \exp\left(\beta_0 + \beta_1 x_{ij} + \cdots\right) = \exp(\beta_0) \times \exp(\beta_1 x_{ij}) \times \cdots$$

Marginal and subject-specific interpretations of a mixed effects model

In a mixed effects model the use of a link function other than the identity link tends to complicate things. To see why this happens I begin with a normal random intercepts model and an identity link and contrast this situation with a binomial random intercepts model and a logit link.

Identity link

A normal random intercepts model with an identity link is a multilevel model with two levels. We have

$$Y_{ij} = \beta_0 + \beta_1 x_{ij} + u_{0i} + \varepsilon_{ij}$$
$$u_{0i} \sim \text{Normal}\left(0, \tau^2\right)$$
$$\varepsilon_{ij} \sim \text{Normal}\left(0, \sigma^2\right)$$

Here i denotes the level-2 unit (the cluster) and j denotes the observation on that level-2 unit. The model for the mean is the following.

$$\mu_{ij} = \underbrace{\beta_0 + \beta_1 x_{ij}}_{\substack{\text{fixed effects} \\ \text{portion}}} + \underbrace{u_{0i}}_{\text{random effect}}$$

So the mean consists of two components: a fixed effects portion and a random effects portion. The fixed effects portion can be interpreted in two distinct ways.

1. The fixed effects portion corresponds to the mean response of an individual for whom $u_{0i} = 0$. So, the fixed effects portion is the average response of an individual that lies at the center of the random effects distribution. This is a subject-specific interpretation of the mixed effects model because it focuses on the behavior of a specific subject.
2. A second interpretation can be obtained by averaging across subjects in the equation for the mean. Formally this is done by integrating both sides of the equation with respect to the random effects distribution.

$$\int \mu_{ij}\, du_{0i} = \int \left(\beta_0 + \beta_1 x_{ij} + u_{0i}\right) du_{0i}$$
$$= \beta_0 + \beta_1 x_{ij} + \int u_{0i}\, du_{0i}$$
$$= \beta_0 + \beta_1 x_{ij}$$

The last step follows because the expectation (mean) of the random effects distribution is zero by assumption, $\int u_{0i}\, du_{0i} = 0$. Thus we see that the fixed effects portion is also the average mean across subjects. This is referred to as the marginal interpretation of the mixed effects model. When the data are a random sample from a known population the marginal interpretation of the fixed effects portion is also called the population-averaged interpretation.

Thus in a mixed effects model with an identity link there are two distinct models for the mean. There is the

marginal (population-averaged) model: $\beta_0 + \beta_1 x_{ij}$, and the

subject-specific model: $\beta_0 + \beta_1 x_{ij} + u_{0i}$

These models are different except for one subject, namely a subject for whom $u_{0i} = 0$. Correspondingly the marginal model has both a marginal interpretation (it is the average across individuals) and a subject-specific interpretation (it is the mean of the individual at the center of the random effects distribution). When we use an identity link we get both of these interpretations for the mean response. When the link function is something other than the identity link, the marginal interpretation of the mean breaks down.

Logit link

Consider a generalized linear mixed effects model (GLMM) in which the response has a binomial distribution and we model the probability of success with a logit link. For simplicity we use the same random intercepts model that was used for the normal model with identity link.

$$\text{logit}\left(p_{ij}\right) = \log \frac{p_{ij}}{1 - p_{ij}} = \beta_0 + \beta_1 x_{ij} + u_{0i}$$

Let's try once again to interpret the fixed effects component of the model. With a logit link for the mean we can apply the inverse logit function

$$\text{inverse.logit}(u) = \frac{\exp(u)}{1 + \exp(u)}$$

to express the mean, the probability of success p_{ij}, as a function of the linear predictor.

$$p_{ij} = \frac{\exp\left(\beta_0 + \beta_1 x_{ij} + u_{0i}\right)}{1 + \exp\left(\beta_0 + \beta_1 x_{ij} + u_{0i}\right)}$$

Subject-specific interpretation

If we set $u_{0i} = 0$ in the logit link equation we see that the fixed effects portion, $\beta_0 + \beta_1 x_{ij}$, represents the logit of an individual that lies at the middle of the random effects distribution on the logit scale.

$$\text{logit}\left(p_{ij}\right) = \beta_0 + \beta_1 x_{ij}$$

Inverting the logit yields

$$p_{ij} = \frac{\exp\left(\beta_0 + \beta_1 x_{ij}\right)}{1 + \exp\left(\beta_0 + \beta_1 x_{ij}\right)}$$

In the subject-specific interpretation the inverse logit of the fixed effect portion is the probability of success of an individual that lies at the middle of the random effects distribution on a logit scale.

Marginal interpretation

To obtain the marginal interpretation we need to average across individuals, i.e., average over the random effects distribution. Thus we have

$$\int \text{logit}\left(p_{ij}\right) du_{0i} = \int \left(\beta_0 + \beta_1 x_{ij} + u_{0i}\right) du_{0i} = \beta_0 + \beta_1 x_{ij}$$

So the fixed effects portion represents the average individual logit. What is its relationship to the average probability of success, i.e., the average value of p? Now we're stuck because the inverse logit of this expression is not equal to the average value of p.

$$\frac{\exp\left(\beta_0 + \beta_1 x_{ij}\right)}{1 + \exp\left(\beta_0 + \beta_1 x_{ij}\right)} = \text{inverse.logit}\left(\int \text{logit}\left(p_{ij}\right) du_{0i}\right) \neq \int p_{ij}\, du_{0i}$$

The problem is the same one we had when we tried to back-transform the regression equation for the mean of a transformed response variable. The operation of taking the mean (the integral in this case) lies between the link function and its inverse, and so the logit and inverse logit do not formally cancel. As a result back-transforming the marginal logit of p does not yield the marginal value of p.

The use of the logit link function in a mixed effects model messes up the marginal interpretation of the fixed effect terms. With an identity link the regression mean has both a subject-specific interpretation and a marginal interpretation. When the link is not the identity, the back-transformed linear predictor still has a subject-specific interpretation, but not a marginal one. This means that the p that corresponds to the mean of $\text{logit}(p)$ is not also the mean of p.

Problems with the subject-specific interpretation of a mixed effects logit model

Without a true marginal interpretation for the fixed effects portion of the mixed effects model, is the subject-specific interpretation enough? In most cases the answer is no. Consider a hierarchical logit model that contains both a level-1 (individual-level) predictor x and a level-2 (group-level) predictor z.

$$\text{logit}\left(p_{ij}\right) = \beta_0 + \beta_1 x_{ij} + \beta_2 z_i + u_{0i}$$

The coefficient β_1 of x has a useful subject-specific interpretation because x can vary within a subject. For a given subject (a fixed value of u_0) if the variable x increases by one unit then the logit increases by β_1 units. The coefficient of z on the other hand does not have a sensible subject-specific interpretation. The variable z is constant within a subject, so unlike x it cannot change when u_0 is held fixed. In order for z to change we need to switch to another subject, but if we do so the random effect u_0 also changes. As a result the observed change in the logit will be due to both a change in z and a change in u_0. To obtain a subject-specific interpretation of β_2 we are forced to concoct a rather fanciful scenario. If two individuals have exactly the same value of the random effect u_0 but their value of z differs by one unit, then β_2 tells us how much the logit is predicted to differ between those two individuals.

Even if we're willing to engage in the mental gymnastics needed to give a subject-specific interpretation to the coefficients of group-level variables, we still can't treat the coefficient as indicating a change in the population average. The logit transformation maps proportions in the interval $(0, 1)$ to logits on the interval $(-\infty, \infty)$. If the distribution of a set of proportions is skewed (lots of values near zero or lots of values near one), the distribution of the logits will be even more skewed. This means that if we average the logits and back-transform this average to a proportion we end up with a value that is more extreme (closer to 0 or closer to 1) than if we just averaged the proportions. The upstart is that the marginal value and the subject-specific value of the regression coefficient of a group-level predictor in a logit model can be widely different.

The distinction between the subject-specific and marginal interpretations of mixed effects models with non-identity links has received extensive treatment in the statistical literature. A discussion of these issues aimed at ecologists can be found in Fieberg et al. (2009).

A marginal approach to generalized linear models

As appealing as mixed effects models are for handling hierarchical clustered/correlated data, the difficulty in

interpreting the parameter estimates from generalized linear mixed effects models with non-identity links suggests that other approaches are needed. One of the most popular of these is generalized estimating equations (GEE). GEE extends generalized linear models to correlated data but differs from mixed effects models in that GEE explicitly fits a marginal model to data. To understand the motivation behind GEE we need to take a closer look at the theory behind generalized linear models.

An abstract formulation of the generalized linear model

The probability distributions used in generalized linear models are related because they are all members of what's called the exponential family of distributions. The density (mass) function of any member of the exponential family takes the following form.

$$f(y; \theta, \phi) = \exp\left[\frac{y\theta - b(\theta)}{a(\phi)} - c(y, \phi) \right] \tag{1}$$

The functions a, b, and c in the formula will vary from distribution to distribution. The parameter θ is called the canonical parameter and is a function of μ. This function is referred to as the canonical link function. The canonical link functions for three members of the exponential family of probability distributions are shown below.

$$\text{Normal: } \theta = \mu$$
$$\text{Poisson: } \theta = \log \mu$$
$$\text{Binomial: } \theta = \log \frac{\mu}{1 - \mu}$$

These in turn are the usual link functions used in normal, Poisson, and logistic regression. The mean and variance of a distribution in the exponential family are given generically as follows.

$$\mu = b'(\theta)$$
$$\text{Var}(y) = a(\phi)b''(\theta) = a(\phi)\frac{d\mu}{d\theta} \equiv a(\phi)\text{Var}(\mu)$$

The last step defines $\text{Var}(\mu)$ as the derivative of the mean with respect to the canonical parameter.

Suppose we have a random sample of size n from a member of the exponential family of distributions. The likelihood is given by

$$L(\mathbf{y}) = \prod_{i=1}^{n} \exp\left[\frac{y_i \theta - b(\theta)}{a(\phi)} - c(y_i, \phi) \right]$$

with corresponding log-likelihood

$$\log L(\mathbf{y}) = \sum_{i=1}^{n} \left(\frac{y_i \theta - b(\theta)}{a(\phi)} - c(y_i, \phi) \right).$$

To find maximum likelihood estimates analytically we take the derivative of the log-likelihood with respect to the canonical parameter θ, set the result equal to zero, and solve for θ.

$$\frac{d}{d\theta}\log L(\mathbf{y}) = 0$$

Typically we do this in a regression setting in which we express the canonical parameter as a linear combination of predictors.

$$\theta = \beta_0 + \sum_{j=1}^{p}\beta_j x_j$$

So, in this case we would differentiate the log-likelihood with respect to each of the regression parameters separately, set the result equal to zero, and solve for the regression parameters. The shorthand notation for this is to use a vector derivative (gradient).

$$\frac{d}{d\boldsymbol{\beta}}\log L(\mathbf{y}) = 0$$

After some algebraic simplification and using the notation defined previously, we end up with $p + 1$ equations of the following form.

$$\frac{\partial}{\partial\beta_j}\log L(\mathbf{y}) = \sum_{i=1}^{n}\frac{y_i - \mu_i}{a(\phi)\mathrm{Var}(\mu_i)}\frac{\partial\mu_i}{\partial\beta_j} = 0 \tag{2}$$

These are referred to as estimating equations because we can use them to obtain the maximum likelihood estimate of $\boldsymbol{\beta}$.

The $p + 1$ estimating equations defined by eqn (2) can be written more succinctly using matrix notation. Define the $n \times (p + 1)$ matrix $\mathbf{D}$, the $n \times n$ matrix $\mathbf{V}$, and the $n \times 1$ vector $\mathbf{y} - \boldsymbol{\mu}$ as follows.

$$\mathbf{D} = \begin{bmatrix} \dfrac{\partial\mu_1}{\partial\beta_0} & \dfrac{\partial\mu_1}{\partial\beta_1} & \cdots & \dfrac{\partial\mu_1}{\partial\beta_p} \\ \dfrac{\partial\mu_2}{\partial\beta_0} & \dfrac{\partial\mu_2}{\partial\beta_1} & \cdots & \dfrac{\partial\mu_2}{\partial\beta_p} \\ \vdots & \vdots & \ddots & \vdots \\ \dfrac{\partial\mu_n}{\partial\beta_0} & \dfrac{\partial\mu_n}{\partial\beta_1} & \cdots & \dfrac{\partial\mu_n}{\partial\beta_p} \end{bmatrix}, \quad \mathbf{V} = a(\phi)\begin{bmatrix} \mathrm{Var}(\mu_1) & 0 & \cdots & 0 \\ 0 & \mathrm{Var}(\mu_2) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \mathrm{Var}(\mu_n) \end{bmatrix}, \quad \mathbf{y} - \boldsymbol{\mu} = \begin{bmatrix} y_1 - \mu_1 \\ y_2 - \mu_2 \\ \vdots \\ y_n - \mu_n \end{bmatrix}$$

With these definitions the $p + 1$ estimating equations of eqn (2) can be written as the following single matrix equation.

$$\begin{bmatrix} \dfrac{\partial \log L}{\partial \beta_0} \\ \vdots \\ \dfrac{\partial \log L}{\partial \beta_p} \end{bmatrix} = \mathbf{D}^T \mathbf{V}^{-1} (\mathbf{y} - \boldsymbol{\mu}) = \mathbf{0} \tag{3}$$

From estimating equations to generalized estimating equations (GEE)

The primary problem in dealing with correlated data in a likelihood framework is that the likelihood becomes inordinately complicated. Generalized estimating equations gets around this difficulty by making the following simple observation. Although the likelihood in eqn (1) depends specifically on the form of the probability distribution, i.e., the functions a, b, and c, the estimating equation that we obtain by differentiating the log-likelihood shown in eqns (2) and (3), depends on the probability distribution only via the mean $\boldsymbol{\mu}$ and the variance $\mathbf{V}$. The rest of the details about the nature of the original probability distribution are irrelevant. So, when a probability model is a member of the exponential family we don't need the all the details of the probability distribution in order to estimate the parameters of a regression equation, just its mean and variance.

Inspired by this observation, generalized estimating equations performs an end-around the likelihood. Rather than starting with eqn (1), GEE starts with the estimating equations in eqn (2), or equivalently the matrix version eqn (3), and generalizes it in two distinct ways.

1. With independent data the matrix $\mathbf{V}$ in eqn (3) is a diagonal matrix. A generalization to correlated data is to instead let $\mathbf{V} = \boldsymbol{\Sigma}$, an arbitrary variance-covariance matrix. Specifically we let

$$\boldsymbol{\Sigma} = a(\phi)\mathbf{S}^{\frac{1}{2}} \mathbf{R}\ \mathbf{S}^{\frac{1}{2}}$$

   where $\mathbf{S}$ is a diagonal matrix and $\mathbf{R}$ is the proposed correlation matrix for our data. Typically $\mathbf{R}$ will depend on parameters that need to be estimated from the data when solving eqn (3). If so, an additional estimating equation will be required.

2. GEE allows us to avoid specifying a probability model entirely. Instead we just need a regression model for the mean μ and a variance model $\mathrm{Var}(\mu)$. The variance model may include a correlation structure or not. For instance we might choose a binomial-like model for the variance, $p(1 - p)$, even though the data themselves are not binomial and perhaps not even discrete!

Both of these two generalizations lead to what is called a generalized estimating equation. Parameter estimates are obtained by solving the generalized estimating equations numerically typically using an optimization algorithm based on Newton's method.

Quasi-likelihood

The estimating equation of eqn (1) is the derivative of the log-likelihood set equal to zero.

$$\frac{\partial}{\partial \beta_j} \log L(\mathbf{y}) = \sum_{i=1}^{n} \frac{y_i - \mu_i}{a(\phi)\mathrm{Var}(\mu_i)} \frac{\partial \mu_i}{\partial \beta_j}$$

From calculus we know that the process of differentiation can be reversed by integrating (antidifferentiating) this expression. Because we can add an arbitrary constant to an antiderivative and obtain another antiderivative, antidifferentiation does not yield a unique result. Antidifferentiating the estimating equation yields the following.

$$\int \frac{\partial}{\partial \beta_j} \log L(\mathbf{y}) d\beta_j = \int \sum_{i=1}^{n} \frac{y_i - \mu_i}{a(\phi) \mathrm{Var}(\mu_i)} \frac{\partial \mu_i}{\partial \beta_j} d\beta_j$$

$$= \sum_{i=1}^{n} \int \frac{y_i - \mu_i}{a(\phi) \mathrm{Var}(\mu_i)} d\mu_i$$

If we start with this last integral, there are two possible scenarios.

1. If the integrand was obtained from an estimating equation that was derived from a log-likelihood then the integral can be written in the form $\log L(\mathbf{y}) + K$ where K contains terms that don't involve μ. So, the log-likelihood will be included in the set of antiderivatives obtained from the estimating equation.

2. If instead we start with a generalized estimating equation by adding a correlation structure to an estimating equation, by postulating a mean-variance relationship Var(μ), or by doing both, then there is no corresponding log-likelihood. Integrating the estimating equation in this case will not yield a true log-likelihood, but instead gives a quantity referred to as a quasi-likelihood (although it might be better to call it a quasi-loglikelihood). The formal definition of the quasi-likelihood is that it is the antiderivative of the generalized estimating equation evaluated at the parameter estimates, eqn (4).

$$Q(y; \hat{\mu}) = \int^{\hat{\mu}} \frac{y_i - \mu}{a(\phi) \mathrm{Var}(\mu)} d\mu \tag{4}$$

The connection between quasi-likelihood and likelihood theory is actually quite close. It turns out that GEE estimates have the same large sample properties that MLEs do—they're consistent, asymptotically normal, etc. In addition, the quasi-likelihood can be generalized to an AIC-like quantity for use in model selection.

Implementing GEE in practice

When estimating a regression model using maximum likelihood (for instance fitting a generalized linear model) we specify a model for the mean and a probability model (along with a link function) for the response. When fitting a model using generalized estimating equations we specify a regression model for the mean, a model for the mean-variance relationship Var(μ), and a model for the correlation. In most GEE software the mean-variance relationship is identified by specifying, using a family argument, a probability model that has the same mean-variance relationship as the one desired. This convention is rather counterintuitive given that there is no probability model in GEE. Table 1 lists some typical choices for the family argument in GEE and the corresponding expression for Var(μ) that results from that choice.

Table 1 Common mean-variance relationships in GEE

Var(μ)	Family
1	gaussian (normal)
μ	poisson

$\mu(1-\mu)$	binomial (Bernoulli)
μ^2	gamma

Depending on the software, a scale parameter φ can also be estimated to account for over- or under-dispersion in Poisson and binomial models.

Table 2 defines some of the common correlation models that are available in GEE software. (The exact name used will depend on the software.) The correlation requested in GEE is referred to as the working correlation and for 2-level hierarchical data it refers to the correlation among observations j and k coming from the same level-2 unit i. Typically there is also an ID argument that is used to identify the variable that denotes the level-2 units.

Table 2 Common correlation structures in GEE

Correlation type	Correlation formula
independence	$\mathrm{cor}\left(Y_{ij},Y_{ik}\right)=0,\ j\neq k$
exchangeable	$\mathrm{cor}\left(Y_{ij},Y_{ik}\right)=\rho,\ j\neq k$
AR(1)	$\mathrm{cor}\left(Y_{ij},Y_{ik}\right)=\rho^{|j-k|},\ j\neq k$
unstructured	$\mathrm{cor}\left(Y_{ij},Y_{ik}\right)=\rho_{jk},\ j\neq k$
user-defined	Specific values are entered for the correlations

Comparing GEE to GLM

1. Typically, GEE returns parameter estimates that are fairly close to those returned by GLM when the models being compared assume the same mean-variance relationship, i.e., use the same value of the family argument.
2. When there is a hypothesized correlation structure in a GEE model, the estimated variance of the parameter estimates tends to be larger in GEE than it is for GLM.
3. Because GEE is not a likelihood-based method, GEE output does not include a log-likelihood, likelihood ratio tests, or AIC. Reported significance tests are the Wald tests for individual parameter estimates.

The quasi family of models

The family argument of the glm function of R permits the use of quasibinomial, quasipoisson, or the more general quasi function. These are not probability distributions per se but are ways to specify a model for Var(μ) in the manner described in Table 1 above. The quasipoisson and quasibinomial choices generalize the expressions given in Table 1 as follows.

Table 3 The quasi values for the family argument

Family	Var(μ)
quasipoisson	$\varphi\mu$
quasibinomial	$\varphi\mu(1-\mu)$

Here $\phi = \dfrac{\text{Pearson deviance}}{\text{df}}$ is called the dispersion parameter. The Pearson deviance is the sum of the squared Pearson residuals. The quasi function can be used to specify these same variance structures as well as others by giving a formula for the variance along with a link function. For instance, `family=quasi(var="mu(1-mu)", link=logit)` yields the same result as `family=quasibinomial`.

The quasipoisson and quasibinomial families provide a crude way to adjust for overdispersion in data, where overdispersion is defined as deviation from the Poisson or binomial probability models due to clumping. When either family = quasipoisson or family = quasibinomial is specified, the parameter estimates one gets from glm are identical to what one gets with family = poisson or family = binomial, but the standard errors are adjusted by multiplying them by the square root of φ.

Full-fledged GEE, on the other hand, assumes the data have a hierarchical structure in which the clusters are identified explicitly with an ID variable. GEE also allows you to model the correlation in a cluster by using one of the correlation structures of Table 2.

Choosing a correlation structure

There are three recommended methods for choosing a correlation structure for GEE (Hardin & Hilbe, 2003).

1. Choose a correlation structure that reflects the manner in which the data were collected. For instance with temporal data a sensible correlation structure is one that includes time dependence, such as AR(1).
2. Choose a correlation structure that minimizes Pan's QIC. QIC is a statistic that generalizes AIC to GEE but is used only for comparing models that are identical except for their different correlation structures. Note: This is not QAIC that is described in Burnham & Anderson (2002).
3. Choose a correlation structure for which the sandwich estimates of the variance most closely approximate the naive estimate of the variance.

I examine the last two options in more detail.

Method 2: Pan's QIC or CIC

QIC is due to Pan (2001) and comes in two flavors. One version is used for selecting a correlation structure and the second version is used for choosing models all of which were fit with the same correlation structure. I first discuss the version of QIC that is used for choosing a correlation structure.

In what follows let *R* denote the correlation structure of interest and let *I* denote the independence model. Recall the definition of AIC.

$$\text{AIC} = -2\log L + 2K$$

QIC is defined analogously as follows.

$$\text{QIC} = -2\underbrace{Q\left(\hat{\beta}(R), \text{I}, \text{Data}\right)}_{\text{quasi-likelihood}} + 2\,\text{trace}\left(\hat{\boldsymbol{\Omega}}_I \hat{\mathbf{V}}_R\right) \tag{5}$$

The first term contains the quasi-likelihood as given in eqn (4) except that it is now extended to the full data set.

$$Q(y; \hat{\mu}) = \sum_{i=1}^{n} \int^{\hat{\mu}_i} \frac{y_i - \mu_i}{a(\phi)\text{Var}(\mu_i)} d\mu_i$$

The quasi-likelihood defined in this formula is actually a bit of a hybrid. For $\hat{\mu}$ we use the regression coefficient estimates obtained from a GEE model with correlation model R, but for Var(μ) we assume a working correlation structure of independence I. Table 4 gives the quasi-likelihood formulas (multiplied by ϕ) for models in which the mean-variance relationship has the form of a binomial or a Poisson random variable.

Table 4 Quasi-likelihoods

Family	Var(μ)	$\phi \cdot Q(\hat{\mu}, \text{I}, \text{Data})$
binomial	$\mu(1 - \mu)$	$\sum_{i=1}^{n} \left[y_i \log \frac{\hat{\mu}_i}{1 - \hat{\mu}_i} + \log(1 - \hat{\mu}_i) \right]$
Poisson	μ	$\sum_{i=1}^{n} \left[y_i \log \hat{\mu}_i - \hat{\mu}_i \right]$

For binary data (binomial with $n = 1$) the estimate of ϕ described above is not used; instead ϕ is set to one. The second term of QIC is a penalty term that is analogous to $2K$ in the formula for AIC. It is defined as follows.

1. Trace refers to "matrix trace", the sum of the diagonal entries of a matrix.
2. $\Omega_I = \mathbf{A}_I^{-1}$ where $\mathbf{A}_I$ is the variance-covariance matrix of the parameter estimates in which an independence model I is used for the correlation.
3. $\hat{\mathbf{V}}_R$ is the modified sandwich estimate (explained in the next section) of the variance-covariance matrix of the parameter estimates that is obtained using the hypothesized correlation model R. The sandwich estimate of the variance-covariance matrix is part of the standard output from GEE.

So, to calculate QIC we need to fit two models: one that uses the correlation model R and the other that uses the independence model I. QIC is then used like AIC. We make various choices for R and choose the R that yields the lowest value of QIC.

Pan (2001) also suggested another version of QIC for comparing models that have the same working correlation matrix R and the same quasi-likelihood form (for instance, all Poisson), but involve different predictor sets. He suggested calculating a statistic QIC_u that is defined as follows.

$$\text{QIC}_u = -2Q\left(\hat{\beta}(p), \text{I}, \text{Data}\right) + 2p$$

Models with smaller values of QIC_u are to be preferred.

Recently QIC has been criticized as a model selection tool, particularly if the model for the mean does not fit the data very well. Hin and Wang (2009) argue that the two terms in the expression for QIC in eqn (5) are not equally informative for correctly identifying the correlation structure. In particular the quasi-likelihood term corresponds to an apparent error rate that better indicates an inadequacy in the mean model rather than in the correlation model. Through simulations they demonstrate that when the mean model is misspecified, the quasi-likelihood term can mask differences in model quality that are due purely to the different assumptions made about the correlation. As a

result they recommend using just the second term of QIC (without the superfluous multiplier of two) when comparing models with different correlation structures. They call this statistic the correlation information criterion, CIC.

$$CIC = \text{trace}\left(\hat{\mathbf{\Omega}}_I \hat{\mathbf{V}}_R\right)$$

Method 3: Comparing sandwich estimates

All GEE packages return something that is variously referred to as the sandwich variance estimate or the robust variance estimate. For many packages this is the default estimate that is displayed in the standard error column of the summary table of the model. The sandwich estimate corrects the variance estimate that is based on the working correlation matrix R using a correction that is constructed from the model residuals. It tends to be robust to an incorrectly specified working correlation model R and will be nearly correct even if R is incorrect. The sandwich estimate is known to behave best for a large sample consisting of many small groups so that there are not too many observations in each group. If the total number of groups is small, the sandwich estimate can be very biased.

In addition to the sandwich variance estimate, GEE packages also return a variance estimate that is based only on the working correlation model R. This is variously called the model-based variance estimate or the naive variance estimate.

A correlation model R can be selected as follows. Fit a series of models that differ only in the choice of correlation matrix R; all of the remaining features of these models are the same. For each model compare the sandwich variance estimates with the model-based variance estimates. The model whose sandwich variance estimates most closely resembles its model-based variance estimates is the one with the best correlation model R.

A problem with GEE and binary data

In addition to invertibility and positive definiteness, correlation matrices for binary data have a further feasibility requirement (Chaganty and Joe 2004). The predicted probabilities of a pair of binary response variables impose a constraint on the legal values that the correlation can take. Let y_i and y_j be two binary observations, let p_i and p_j be their predicted probabilities under a given model, and let r_{ij} be their correlation as estimated from say a semivariogram model. Prentice (1998) derived the following formula for the joint probability of the binary pair y_i and y_j.

$$P\left(y_i, y_j\right) = p_i^{y_i}\left(1 - p_i\right)^{y_i} p_j^{y_j}\left(1 - p_j\right)^{y_j}\left[1 + r_{ij}\frac{\left(y_i - p_i\right)\left(y_j - p_j\right)}{\sqrt{p_i p_j\left(1 - p_i\right)\left(1 - p_j\right)}}\right]$$

Because probabilities must be non-negative, the expression inside the brackets imposes a constraint on the possible values the correlation r_{ij} can take.

Currently available GEE software, including the gee and geepack packages of R, do not check for the feasibility of the correlation matrices they estimate for binary data. The general consensus is that if a correlation estimated by GEE is infeasible that is a good reason to reject that correlation model. There has been a lot of discussion of this issue in the biomedical and biostatistical literature. For a recent survey see Ziegler and Vens (2010) as well as the discussion that follows the article (Breitung et al. 2010; Shults 2011).

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