# Growth Curve Models of Repeated Binary Response

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## SUMMARY

Experimental designs that include repeated measures of binary response variables over time and under different conditions are common in biology. In such settings, it is often desirable to characterize the response pattern over time. When response variables are continuous, this characterization can be made in terms of a growth model such as the Potthoff–Roy growth curve model. We illustrate how a similar growth curve modeling strategy can be implemented using weighted least squares (WLS) methods for binary response data. The growth models are constructed in terms of polynomial functions across marginal response. However, when growth models are fit to repeated binary response, the nonsignificant higher-order polynomial functions are dropped from the model, rather than used as covariates. Dropping the nonsignificant polynomials from the model will reduce the number of response functions, and help avoid small-sample problems that can occur when the number of correlated response functions is large and sample sizes are small. The reduced set of response functions are then modeled using WLS methods. We illustrate such models with an example of binary fly oviposition response (accept or reject) exhibited by two populations of flies at four ages to two types of fruit.

## 1. Introduction

Experimental designs with repeated measures over time permit evaluation of maturation, resistance, and chronic dose, in addition to fixed group effects. Split-plot repeated-measures designs enable comparison of response curves for two or more treatments based on the within-subject component of variance. The principal outcome variables in such designs are often binary. For example, in a study of host fruit acceptance for oviposition by adult female flies, individual flies from two different populations were each exposed to two test fruits at ages 8–9 days, 11–12 days, 15–16 days, and 18–19 days, with oviposition (yes, no) recorded for each fly at each age. Objectives for data analysis include quantifying the effect of fly origin and test fruit on oviposition, as well as characterizing the effect of maturation over time. The impact of maturation on fly origin and test fruit effects was also of interest.

Such repeated-measures designs are based on fewer subjects and have more measures per subject than similar completely randomized designs. When time corresponds to one of the dimensions of the repeated measures, responses can often be characterized by a reduced set of functions (such as polynomial functions). Such growth models have been considered for Gaussian response by Potthoff and Roy (1964), Khatri (1966), and Rao (1965, 1966,

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1967), and account for the correlated response of a subject's measures over time. These models and methods have been summarized by Grizzle and Allen (1969), Timm (1980), Woolson and Leeper (1980), and Geisser (1980). We present similar methods appropriate for fitting growth models to repeated measures of binary response.

When repeated binary measures are made over time, several methods have been proposed for model fitting. A general modeling method for repeated binary response analogous to the general multivariate linear model for continuous response was proposed by Koch et al. (1977). This method is an extension of the weighted least squares (WLS) method of Grizzle, Starmer, and Koch (1969). Models can be fit using this method to transition probabilities and marginal proportions, with examples of applications given by Koch et al. (1977), Stanish and Koch (1984), and in the *SAS User's Guide* (1985).

Although the WLS approach is flexible, problems arise when there are continuous covariables, small sample sizes, or moderate amounts of missing data. Other methods have been developed that address these situations. Partial-association tests based on a generalized Mantel–Haenszel strategy have been proposed by Landis, Heyman, and Koch (1978) and Landis et al. (1988). Stiratelli, Laird, and Ware (1984) have developed two-stage random-effect models for repeated binary response which are fit using an iterative EM algorithm. These models are similar to those presented by Laird and Ware (1982) for Gaussian response. In work as yet unpublished, Stram, Wei, and Ware have extended this approach to settings with ordered categorical outcomes, missing data, and time-dependent covariates. Zeger and Liang (1986) and Liang and Zeger (1986) have developed methods for repeated binary response that are fit using quasi-likelihood methods. Such models can be fit by iterative reweighted least squares using GLIM (Baker and Nelder, 1978) software. Korn and Whittemore (1979) have proposed a conditional model for repeated measures of binary data. Variance component models for binary response have been proposed by Anderson and Aitkin (1985) and Beitler and Landis (1985). Recent reviews of this literature are given by Koch et al. (1980) and Ware, Lipsitz, and Speizer (1988). Also, see Ware (1985) for a similar review in the context of repeated measures of a continuous outcome.

We extend application of the WLS method of Koch et al. (1977) to settings where the number of repeated measures is too large (relative to the sample size) to permit modeling all marginal response functions. The method is analogous to growth curve models with continuous response, and uses a polynomial representation of response over time to exclude nonsignificant higher-order response functions. Subsequent analyses are based on the reduced set of response functions. The method is illustrated with an example of repeated measurement of oviposition responses of *Rhagoletis pomonella* (Walsh) adult female flies to two test fruit at four ages.

## 2. Fitting Potthoff–Roy Growth Models to Binary Repeated Measures Using WLS

The basic development of weighted least squares methods for repeated-measures models is given by Koch et al. (1977) and summarized in the Appendix. In this section, we illustrate how a Potthoff–Roy (1964) growth model can be fit to repeated measures of binary data using the WLS approach. Assume $d$ repeated measures of a binary response are made for $n_i$ study units in $i$ subpopulations ($i = 1, \ldots, s$) resulting in $r = 2^d$ possible response profiles. Let $\mathbf{p}_i$ denote an $r \times 1$ vector of observed response proportions, so that $\mathbf{n}_i \mathbf{p}_i$ will follow a multinomial distribution with parameter $\boldsymbol{\pi}_i$. We specify linear models for a column concatenation of $u_i$ ($u_i < r$) differentiable functions of $\mathbf{p}_i$, $\mathbf{F}_i = \mathbf{f}_i(\mathbf{p}_i)$, where $\mathbf{F} = (\mathbf{F}_1' \ \mathbf{F}_2' \ldots \mathbf{F}_s')'$ such that $\mathbf{F} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$, and fit these models using WLS.

For simplicity, assume that each vector of functions $\mathbf{F}_i$ ($i = 1, \ldots, s$) corresponds to the $(T + 1)$ marginal response functions at times $t_j$ ($j = 0, 1, \ldots, T$) in each subpopulation, where $u_i = (T + 1)$ for all $i = 1, \ldots, s$. Let $\mathbf{N}$ denote a $(T + 1) \times (q + 1)$ matrix of natural

polynomials [with $j$th row $(1 \; t_j \; t_j^2 \; \ldots \; t_j^q)$] for all $i = 1, \ldots, s$. Then a polynomial model (of order $q$ for each subpopulation) is given as

$$\mathbf{F} = (\mathbf{X}_s \otimes \mathbf{N})\boldsymbol{\beta} + \boldsymbol{\varepsilon}, \tag{2.1}$$

where $\otimes$ denotes the left Kronecker product formed by multiplying each element in the left matrix by the matrix on the right, and $\mathbf{X}_s$ is an $s \times v$ full-rank design matrix $(v \leqslant s)$ relating growth across subpopulations. When $q < T$, model (2.1) can be recognized as the row-expanded form of a Potthoff–Roy growth model. Partitioning $\boldsymbol{\beta}$ into $v$ vectors of dimension $(q + 1) \times 1$, $\boldsymbol{\beta}_m$ $(m = 1, \ldots, v)$, and partitioning $\boldsymbol{\varepsilon}$ into $s$ vectors of dimension $(T + 1) \times 1$, $\boldsymbol{\varepsilon}_i$ $(i = 1, \ldots, s)$, we can express model (2.1) in a standard multivariate format as

$$(\mathbf{F}_1 \; \mathbf{F}_2 \; \ldots \; \mathbf{F}_s)' = \mathbf{X}_s(\boldsymbol{\beta}_1 \; \boldsymbol{\beta}_2 \; \ldots \; \boldsymbol{\beta}_v)'\mathbf{N}' + (\boldsymbol{\varepsilon}_1 \; \boldsymbol{\varepsilon}_2 \; \ldots \; \boldsymbol{\varepsilon}_s)'. \tag{2.2}$$

When $\mathbf{X}_s = \mathbf{I}_s$, the function at the $j$th time in the $i$th subpopulation is modeled by the polynomial function

$$F_{ij} = \beta_{i0} + t_j\beta_{i1} + t_j^2\beta_{i2} + \cdots + t_j^q\beta_{iq} + \varepsilon_{ij}.$$

Model (2.2) has the form of a traditional Potthoff–Roy growth model for continuous data. For normally distributed response, Potthoff and Roy (1964) proposed estimating parameters in model (2.2) by transforming the model to a standard multivariate model through postmultiplication by $\mathbf{G}^{-1}\mathbf{N}'(\mathbf{N}'\mathbf{G}^{-1}\mathbf{N})^{-1}$, where $\mathbf{G}$ is an arbitrary symmetric matrix of rank $(T + 1)$. Parameters were subsequently estimated by ordinary least squares. Khatri (1966) and Rao (1965) illustrate that maximum likelihood estimates under a similar conditional model result when $\mathbf{G} = \mathbf{S}$, the sample variance matrix. These models are equivalent to a special type of seemingly unrelated regression (SUR) model based on a column expansion, as illustrated by Stanek and Koch (1985).

Estimation of parameters for the SUR model with continuous data is based on WLS, with weights estimated from residuals of ordinary least squares regressions. The apparent similarity between WLS estimation under SUR models and the WLS used under the modeling framework of Grizzle et al. (1969) is more than casual. The categorical data modeling strategy can be viewed as a direct extension of SUR models and methods to product-multinomial data (Stanek, Institute of Statistics Mimeo Series No. 1456, University of North Carolina, 1984). Categorical data applications of SUR models differ in that separate weighting matrices are estimated for each subpopulation [each row in model (2.2)], and parameter estimates are based on a single iteration of WLS. Estimation for growth models of marginal response functions as in (2.2) is nearly identical for continuous and categorical data.

## 3. Choosing a Subset of Response Functions

The categorical growth model (2.2) is a model for marginal response functions at $(T + 1)$ times based on $q + 1$ $(<T)$ polynomial trends. For continuous data applications, as illustrated by Khatri (1966) and Grizzle and Allen (1969), the additional $(T - q)$ trends serve as covariates. Inclusion of these additional trends is useful in the model if they are correlated with the $(q + 1)$ response trends of interest. However, the inclusion of the $(T - q)$ covariates often lacks a biological rationale, and Kenward (1985) has suggested that selection of covariates based on observed correlations may result in underestimation of true variances. In categorical data applications, excluding the $(T - q)$ covariates not only simplifies interpretation of the model, but also reduces the number of response functions on which the model is based. A reduction in the number of response functions permits

growth models to be fit to repeated-measures categorical data problems with smaller sample sizes.

We illustrate a preliminary model building procedure to arrive at a subset of $q$ polynomial response functions and subsequent modular modeling for categorical data. Orthogonal polynomials are used in the model building to allow for independent testing of polynomial trends, and hopefully reduce the number of modeled functions. The procedure differs from the backward elimination testing strategy for orthogonal polynomial models used with continuous data in that orthogonal polynomial trends in each subpopulation are constructed, and the resulting trends tested directly prior to model fitting. Modular linear models are then constructed for significant trends.

Initially, assume $\mathbf{X}_s = \mathbf{I}_s$ in model (2.2) and let $\mathbf{N}$ represent a full $(T + 1) \times (T + 1)$ matrix of natural polynomials. Orthogonal functions are formed by replacing $\mathbf{N}'$ by the set of orthogonal polynomials, $\mathbf{P}'$, $(\mathbf{P}'\mathbf{P} = \mathbf{I}_{(T+1)})$, where $\mathbf{N}' = \mathbf{R}'\mathbf{P}'$, and then postmultiplying each side of equation (2.2) by $\mathbf{P}$. If we define $\mathscr{F}_k$ as an $s \times 1$ column vector for the $k$th trend such that $\mathscr{F} = (\mathscr{F}_0 \ \mathscr{F}_1 \ \ldots \ \mathscr{F}_T) = (\mathbf{F}_1 \ \mathbf{F}_2 \ \cdots \ \mathbf{F}_s)'\mathbf{P}$; $\mathbf{B}_k$ as the corresponding $s \times 1$ column vector of parameters such that $\mathbf{B} = (\mathbf{B}_0 \ \mathbf{B}_1 \ \cdots \ \mathbf{B}_T) = (\boldsymbol{\beta}_1 \ \boldsymbol{\beta}_2 \ \cdots \ \boldsymbol{\beta}_s)'\mathbf{R}'$; and $\mathbf{e}_k$ as the $s \times 1$ column vector such that $\mathbf{e} = (\mathbf{e}_0 \ \mathbf{e}_1 \ \cdots \ \mathbf{e}_T) = (\boldsymbol{\varepsilon}_1 \ \boldsymbol{\varepsilon}_2 \ \cdots \ \boldsymbol{\varepsilon}_s)'\mathbf{P}$; then model (2.2) simplifies to the model $\mathscr{F} = \mathbf{I}_s\mathbf{B} + \mathbf{e}$.

The $(T + 1)$ column vectors $\mathscr{F}_k$ $(k = 0, \ldots, T)$ represent $T + 1$ orthogonal trends for the $s$ subpopulations. Important trends are identified by direct hypothesis tests for the trend vectors of the form $\mathbf{E}_A(\mathscr{F}_k) = \mathbf{0}$, where $\mathbf{E}_A$ denotes the asymptotic expectation of $\mathscr{F}_k$ (see Landis et al., 1976). The test statistics are given by $Q_k = \mathscr{F}'_k\mathbf{V}_{\mathscr{F}_k}^{-1}\mathscr{F}_k$, which is approximately distributed according to a $\chi^2$ distribution with $s$ degrees of freedom under the null hypothesis.

Each test for trend is constructed directly from the full set of response functions, and not as a contrast subsequent to fitting a model. This testing procedure is advantageous because it reduces the chance that the variance matrix will be singular. The test is based on an estimate of one response function and one variance from each subpopulation. This approach to testing for trend is preferable to the backward elimination procedure [as used for continuous data (Bock, 1975)] since the latter approach would necessitate estimation of the full $(T + 1) \times (T + 1)$ variance matrix for each subpopulation, and as a result be more susceptible to small-sample-size problems. However, when sample sizes in subpopulations are large, simultaneous tests of more than one response function per subpopulation can be constructed, and the backward elimination procedure is feasible.

In many applications, significant trends will consist of a set of low-order polynomial functions, say $q < T$. Modular models can be built directly to a column concatenation of these functions, of the form $\mathscr{F}_k = \mathbf{X}_k\mathbf{B}_k + \mathbf{e}_k$, for $k = 0, 1, \ldots, q$. Such models are directly analogous to analysis of variance models fit to orthogonal trends when response is continuous. When $\mathbf{X}_k = \mathbf{X}$ (of dimension $s \times v$) for all $k = 0, 1, \ldots, q$, this set of simultaneous models is given as

$$(\mathscr{F}'_0 \ \mathscr{F}'_1 \ \ldots \ \mathscr{F}'_q)' = (\mathbf{I}_{q+1} \otimes \mathbf{X})(\mathbf{B}'_0 \ \mathbf{B}'_1 \ \ldots \ \mathbf{B}'_q)' + (\mathbf{e}'_0 \ \mathbf{e}'_1 \ \ldots \ \mathbf{e}'_q)',$$

and can be recognized as the column-expanded form of a Potthoff–Roy growth model in which all covariates have been dropped. When the design matrices $\mathbf{X}_k$ differ, the model is a more general SUR model, as discussed by Stanek and Koch (1985).

Once a final model is fit, parameter estimates can be converted back to natural polynomial estimates for each subpopulation. The natural polynomial estimates in each subpopulation are constructed by postmultiplying a matrix of predicted functions by the upper-left $(q + 1) \times (q + 1)$ submatrix of $(\mathbf{R}')^{-1}$, $(\hat{\boldsymbol{\beta}}_1 \ \hat{\boldsymbol{\beta}}_2 \ \cdots \ \hat{\boldsymbol{\beta}}_s)' = (\mathbf{X}_0\hat{\mathbf{B}}_0 \ \mathbf{X}_1\hat{\mathbf{B}}_1 \ \cdots \ \mathbf{X}_q\hat{\mathbf{B}}_q)(\mathbf{R}^*{}')^{-1}$, where $\hat{\boldsymbol{\beta}}_k$ represents a $(q + 1) \times 1$ vector of natural polynomial estimates for the $i$th subpopulation and $(\mathbf{R}^*{}')^{-1}$ is the upper left $(q + 1) \times (q + 1)$ submatrix from $(\mathbf{R}')^{-1}$.

Although the development of previous sections was presented in terms of a simple repeated-measures design where each subject was observed under the same conditions at $T + 1$ times, the methods can readily be extended to factorial repeated-measures designs or crossover designs with repeated measures. In addition, if the response is ordinal rather than binary, similar methods can be applied based on a function of the ordinal response (see Stanek's unpublished mimeo series report for an example).

## 4. An Example of Fly Oviposition

We illustrate these methods with data collected in a study of host fruit acceptance for oviposition by *Rhagoletis pomonella* adult female flies (Diptera: Tephritidae) (Prokopy et al., 1982a, 1982b; Stanek et al., 1987). Individual females originating as larvae from apple or hawthorn were exposed to apple and hawthorn fruit (separately) at ages 8–9, 11–12, 15–16, and 18–19 days after adult eclosion. Each exposure was initiated by gently placing a fly onto a test fruit and allowing it to remain until it either attempted oviposition (scored as an "accepter"), or failed to do so within 5 minutes or left the fruit (scored as a "rejecter"). The experimental design consists of repeated measures of a binary variable under eight conditions ($d = 2$ fruit $\times$ 4 ages) for flies from the two larval origin subpopulations. Hypotheses of interest concern the effect of the flies' age, the larval host origin, and the test fruit. Differences in a host origin or test fruit with fly age are also of interest.

Complete data were obtained on 70 flies (37 of apple and 33 of hawthorn larval origin). Only 30 of the possible $2^8 = 256$ response profiles were observed (Table 1). Simple linear functions of the response profiles were constructed that represent the proportion of accepter responses for each test fruit and age in each subpopulation (Table 2). These proportions correspond to the simple mean response (with scores of $1$ = accepter and $0$ = rejecter) for flies of a larval origin under each of the eight conditions. The response proportions at the four ages for flies of a given larval origin and test fruit are positively correlated (except for apple larval origin flies on hawthorn fruit at days 15–16) (Table 3). Correlations for hawthorn origin flies are generally larger. The correlation of 1.00 for hawthorn larval origin flies tested on apple fruit at 15–16 and 18–19 days indicates an identical response for each

**Table 1**
*Frequency of observed profiles by fly origin for eight binary responses* (A: *Accept*; R: *Reject*)

| | Larval origin | | | Larval origin | |
|---|---|---|---|---|---|
| Profile | Apple | Hawthorn | Profile | Apple | Hawthorn |
| AAAAAAAA | 2 | 1 | RRRAARAA | 1 | 0 |
| AAARAAAA | 1 | 0 | RRRAAAAA | 1 | 0 |
| AARAAAAA | 1 | 0 | RRRRAAAA | 6 | 7 |
| ARAAARAR | 1 | 0 | RRRRRRAR | 1 | 0 |
| ARRRAAAA | 1 | 1 | RRRRRAAA | 3 | 5 |
| RAAAAAAA | 1 | 0 | RRRRARAA | 2 | 1 |
| RAARAAAA | 1 | 0 | RRRRAARR | 1 | 0 |
| RARRAAAA | 1 | 2 | RRRRAARA | 2 | 1 |
| RARRRRAR | 1 | 0 | RRRRRRAA | 2 | 2 |
| RRAARAAA | 2 | 1 | RRRRRRRA | 1 | 6 |
| RRAAARAA | 1 | 0 | RRRRRRRR | 0 | 2 |
| RRARAAAA | 1 | 0 | RRRRRARA | 0 | 1 |
| RRARAARR | 1 | 0 | RRRRRARR | 0 | 1 |
| RRARARAA | 1 | 0 | RRRRARRR | 0 | 1 |
| RRRARRAA | 1 | 0 | RRRRAAAR | 0 | 1 |

*Note:* The order of response is days 8–9, 11–12, 15–16, and 18–19 on apple fruit, followed by analogous response on hawthorn fruit.

**Table 2**
*Observed proportion that accept fruit (standard errors) and predicted values (standard errors) from final model in Section 4*

| Larval origin | Test fruit | Age in days | Observed value (SE) | Predicted value (SE) |
|---|---|---|---|---|
| Apple | Apple | 8–9 | .162 (.061) | .118 (.049) |
|  |  | 11–12 | .216 (.068) | .186 (.043) |
|  |  | 15–16 | .324 (.077) | .278 (.044) |
|  |  | 18–19 | .297 (.075) | .347 (.051) |
| Apple | Hawthorn | 8–9 | .703 (.075) | .667 (.048) |
|  |  | 11–12 | .649 (.078) | .736 (.039) |
|  |  | 15–16 | .865 (.056) | .827 (.036) |
|  |  | 18–19 | .865 (.056) | .896 (.042) |
| Hawthorn | Apple | 8–9 | .061 (.042) | .088 (.038) |
|  |  | 11–12 | .091 (.050) | .083 (.033) |
|  |  | 15–16 | .061 (.042) | .076 (.036) |
|  |  | 18–19 | .061 (.042) | .071 (.043) |
| Hawthorn | Hawthorn | 8–9 | .455 (.087) | .514 (.058) |
|  |  | 11–12 | .636 (.084) | .583 (.049) |
|  |  | 15–16 | .636 (.084) | .674 (.046) |
|  |  | 18–19 | .849 (.062) | .743 (.049) |

**Table 3**
*Summary of correlations (phi coefficients) at different ages by larval origin and test fruit*

|  |  | Hawthorn larval origin flies | | | | Apple larval origin flies | | | |
|---|---|---|---|---|---|---|---|---|---|
|  |  | Age (days) | | | Apple fruit | Age (days) | | | Apple fruit |
|  |  | 8–9 | 11–12 | 15–16 | 18–19 | 8–9 | 11–12 | 15–16 | 18–19 |
| Age (days) | 8–9 |  | .36 | .47 | .47 |  | .48 | .32 | .36 |
|  | 11–12 | .44 |  | .36 | .36 | .26 |  | .34 | .23 |
|  | 15–16 | .44 | .61 |  | 1.00 | −.08 | −.13 |  | .43 |
|  | 18–19 | .05 | .21 | .38 |  | .09 | .21 | .31 |  |
|  |  | Hawthorn fruit | | | | Hawthorn fruit | | | |

*Note:* The correlation matrix for apple fruit is in the upper-right quadrant, and the correlation matrix for hawthorn fruit in the lower-left quadrant.

fly at these times (i.e., the same two flies accept the fruit and the 31 other flies reject the fruit at both ages). This condition is noteworthy because it would result in a singularity in the weight matrix if a backward elimination modeling strategy were employed (Stanek et al., 1987). Although not presented, smaller positive correlations were observed between responses to apple and hawthorn fruit by flies of a given larval origin at different ages.

Since there are a large number of potential response functions, and a small sample size in each larval origin subpopulation, preliminary hypotheses are constructed based on averaging response over levels of other variables. In addition, polynomial models are used to identify a subset of response functions with significant variability. The preliminary hypothesis tests for the main effect of larval origin, test fruit, and larval origin by test fruit interaction are constructed as 1-degree-of-freedom Wald statistics by premultiplication of the vector of observed proportions in Table 2 by

$$\mathbf{A}_1 = (1 \quad -1) \otimes \mathbf{1}_8', \quad \mathbf{A}_2 = (1 \quad -1 \quad 1 \quad -1) \otimes \mathbf{1}_4', \quad \text{and} \quad \mathbf{A}_3 = (1 \quad -1 \quad -1 \quad 1) \otimes \mathbf{1}_4',$$

respectively, where $\mathbf{1}_n$ denotes an $n \times 1$ vector of ones. The results indicate presence of

a significant larval origin effect ($Q = 8.86$, $P = .003$) and a significant test fruit effect ($Q = 187.45$, $P < .001$), but no evidence of a larval origin by test fruit interaction ($Q = .48$, $P = .488$). These tests average response over four ages.

Next we develop a polynomial model for fruit acceptance that identifies trends over time and evaluates the influence of larval origin and test fruit on these trends. Trends are constructed by postmultiplication of the vector of marginal response functions in Table 2 by $A_4 = I_4 \otimes P^*$, where

$$P^* = \begin{bmatrix} 1 & 1 & 1 & 1 \\ -5 & -2 & 2 & 5 \\ 1 & -1 & -1 & 1 \\ -2 & 5 & -5 & 2 \end{bmatrix}.$$

The matrix $P^*$ corresponds to a matrix of orthogonal polynomial functions (not orthonormal), where the orthogonal trends are scaled so that the linear trend represents deviations in days from the midpoint of the study time period. The use of orthogonal (but not orthonormal) polynomials will not affect test statistics because the scaling is accounted for in both the numerator and the denominator, and simplifies interpretation. The hypothesis of no cubic age trend in each larval origin by test fruit group is constructed by premultiplication of the vector of orthogonal polynomial functions by $A_5 = I_4 \otimes (0\ 0\ 0\ 1)$. The resulting 4-degree-of-freedom test statistic is nonsignificant ($Q = 7.212$, $P = .129$). A similar hypothesis for quadratic effects is also nonsignificant ($Q = 1.193$, $P = .879$), whereas hypothesis tests for linear and constant effects are highly significant ($Q = 26.24$, $P < .001$ and $Q = 523.8$, $P < .001$, respectively). These results indicate that a model based on the constant and linear trends is appropriate.

Since the number of flies studied in each larval origin group is small, further analysis is based on four response functions in each subpopulation (a constant and linear trend for apple and hawthorn fruit) rather than the original eight response functions. These response functions are selected and ordered so that all the constant functions appear first, followed by the linear functions, by multiplying the $16 \times 1$ vector of orthogonal functions by

$$A_6 = \begin{bmatrix} I_4 \otimes (1 \quad 0 \quad 0 \quad 0) \\ \hline I_4 \otimes (0 \quad 1 \quad 0 \quad 0) \end{bmatrix}.$$

The resulting functions are fit to a simple modular model with main effects for larval origin and test fruit, and a larval origin by test fruit interaction using the design matrix

$$X = I_2 \otimes \begin{bmatrix} 1 & 1 & 1 & 1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & 1 & -1 \\ 1 & -1 & -1 & 1 \end{bmatrix}.$$

Tests for main effects and interactions for the constant trend (with 1 degree of freedom) indicate evidence of significant larval origin ($Q = 8.86$, $P = .003$) and test fruit ($Q = 187.45$, $P < .001$) effects for the constant function, but no indication of a larval origin by test fruit interaction ($Q = .48$, $P = .488$). Since the constant function corresponds to an average response over time, these test results imply that a simple main effect model will fit mean response. The test results for the linear trend indicate a significant test fruit effect ($Q = 7.76$, $P = .005$), and a significant larval origin by test fruit interaction ($Q = 3.86$, $P = .049$). The larval origin effect for the linear trend is nonsignificant ($Q = .05$, $P = .825$). Inspection of the linear response functions indicates that the interaction is due to a differential response for hawthorn flies on apple test fruit. A subsequent test for parallel slopes among flies on each test fruit and hawthorn flies on hawthorn fruit fails to reject this hypothesis ($Q = 2.20$,

d.f. = 2, $P$ = .334). The resulting reduced model contains main effects for the constant function, and two linear trends. The model is specified using the design matrix

$$\mathbf{X} = \begin{bmatrix} \mathbf{X}_0 & \mathbf{0} \\ \mathbf{0} & \mathbf{X}_1 \end{bmatrix}$$

where

$$\mathbf{X}_0 = \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & -1 \\ 1 & -1 & 1 \\ 1 & -1 & -1 \end{bmatrix} \quad \text{and} \quad \mathbf{X}_1 = \begin{bmatrix} 1 & 0 \\ 1 & 0 \\ 0 & 1 \\ 1 & 0 \end{bmatrix}.$$

The goodness-of-fit statistic for the model ($Q$ = 3.18 with 3 d.f., $P$ = .365) indicates adequate fit. The vector of parameter estimates is given as

$$(\hat{\mathbf{B}}_0' \ \hat{\mathbf{B}}_1') = (1.72 \quad .31 \quad -1.10 \quad 1.33 \quad -.10)$$

with standard deviations given by

$$\mathrm{SD}(\hat{\mathbf{B}}_0' \ \hat{\mathbf{B}}_1') = (.094 \quad .100 \quad .080 \quad .313 \quad .267).$$

The parameter estimates and standard errors can be converted back to parameter estimates for a natural polynomial model for each test fruit in each larval origin subpopulation. Since the design matrices differ for constant and linear trends, the predicted constant and linear functions must first be evaluated before converting back to natural polynomials. These predicted functions are given as

$$(\mathbf{X}_0\hat{\mathbf{B}}_0 \quad \mathbf{X}_1\hat{\mathbf{B}}_1) = \begin{bmatrix} .929 & 1.328 \\ 3.126 & 1.328 \\ .317 & -.098 \\ 2.514 & 1.328 \end{bmatrix}.$$

Since $\mathbf{P}^*$ is orthogonal (but not orthonormal), the natural polynomial estimates are formed by postmultiplying the 4 × 2 matrix of orthogonal polynomial estimates by

$$\begin{bmatrix} \frac{1}{4} & 0 \\ 0 & \frac{1}{58} \end{bmatrix},$$

which represents the 2 × 2 upper-left submatrix from $(\mathbf{R}'\mathbf{D}^{1/2})^{-1}$, where $\mathbf{P}^{*\prime}\mathbf{P}^* = \mathbf{D}$. Predicted values are then estimated by postmultiplying the resulting matrix of natural polynomial estimates by the matrix

$$\begin{bmatrix} 1 & 1 & 1 & 1 \\ -5 & -2 & 2 & 5 \end{bmatrix}.$$

The resulting predicted values and associated standard deviations are given in Table 2. In programs such as GENCAT (Landis et al., 1976) or CATMOD (SAS Institute, 1985), predicted values can be estimated by saving the vector of predicted values and then premultiplying this vector by

$$[\tfrac{1}{4}(\mathbf{I}_4 \otimes \mathbf{1}_4) \,|\, \tfrac{1}{58}(\mathbf{I}_4 \otimes (-5 \quad -2 \quad 2 \quad 5)')].$$

## 5. Discussion

Parallel techniques for analysis of repeated-measures data when a response is continuous or discrete are clearly desirable. As illustrated in Sections 3 and 4, growth-curve-type models are feasible for repeated binary response. Some aspects of the modeling strategy make certain growth-curve-type models particularly appealing for a repeated binary response.

Limiting analyses to response functions that are identified with important variability in the data reduces the sample size required for test statistic asymptotics, minimizes chance collinearity among the marginal proportions and weight matrices, and guards against artificially inflated test statistics (Kenward, 1985). Often, the number of study subjects, $n$, is small relative to the number of time points, $d$, so this reduction is important. In the example, models based on the eight response functions (4 constant and 4 linear) can be used instead of models based on 16 response functions.

Other modeling concerns are similar when a response is binary or continuous. In each setting, a scale choice is desirable that linearizes the trends over time (or dose). Although the present example considered age trends in simple response proportions, similar methods could be applied based on the logarithm of the marginal response, corresponding to a multiplicative scale over age. Another consideration in common for discrete and continuous responses is proper accounting for the repeated-measures covariance structure. Analyses that assume independent repeated responses for subjects produce inflated test statistics. There is a double danger in such models, because the sample size also appears inflated, making large-sample requirements for the test statistics seem more believable.

More generally, the method of Grizzle et al. (1969) can be viewed as an extension of seemingly unrelated regression (SUR) modeling to categorical data (Stanek, unpublished mimeo series report, 1984). Since a special class of SUR models form the class of growth curve models (Stanek and Koch, 1985), there is a direct link between continuous and categorical applications. There are two differences between categorical WLS methods and standard SUR methods, the first of which is just a difference in notation. SUR models are usually expressed in terms of a column expansion of the dependent variables, whereas the categorical WLS framework of Grizzle et al. (1969) is usually developed using a row expansion of the dependent variables (corresponding to the vector of responses in a subpopulation). In addition, SUR models differ from the categorical WLS framework in that the covariance matrix is assumed to be identical for each row of the dependent variables. Under the categorical WLS framework, the covariance matrix differs between rows, since it is estimated from the observed sample response proportions. Both methods use weighted least squares to fit the models, where the weight is based on an estimate of the covariance matrix. Each method can conceptually be iterated, using residuals based on parameter estimates to reestimate the covariance matrix, and then refit the model. Although examples of applications of WLS methods are numerous (Forthofer and Lehnen, 1981), and attempts have been made in econometric literature to generalize SUR models to categorical data (Zellner and Lee, 1965; Zellner and Rossi, 1983), the connection between the methods is not widely appreciated.

### Résumé

Les dispositifs expérimentaux qui incluent des mesures répétées de variables réponses binaires au cours du temps et sous différentes conditions sont fréquents en biologie. Dans de telles situations, il est souvent souhaitable de caractériser le modèle de réponse au cours du temps. Quand les variables réponses sont continues cette caractérisation peut être faite en termes de modèle de croissance comme le modèle de courbe de croissance de Potthoff–Roy. Nous montrons comment une stratégie similaire de modélisation de courbe de croissance sur données binaires peut être mise en oeuvre utilisant les méthodes des moindres carrés pondérés (WLS). Les modèles de croissance sont construits à partir de fonctions polynomiales sur les réponses marginales. Cependant, lorsque les modèles de croissance sont ajustés sur des réponses binaires répétées, les fonctions polynomiales d'ordre élevé non significatives sont éliminées du modèle plutôt que d'être utilisées comme covariables. Eliminer du modèle les polynômes non significatifs réduira le nombre de fonctions réponses et permettra d'éviter les problèmes dus aux faibles tailles d'échantillons qui peuvent se produire lorsque le nombre de fonctions réponses corrélées est grand devant les tailles d'échantillon. L'ensemble réduit de fonctions réponses est alors modélisé suivant la méthode WLS. Nous illustrons de tels modèles avec un exemple de réponse binaire (présence, absence) de ponte produite par 2 populations de mouches en fonction de 2 types de fruits à 4 âges différents.

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## APPENDIX

A general structure for repeated-measures designs using the WLS approach is given by Koch et al. (1977). We briefly review this development for binary response to develop ideas and fix notation. Assume $d$ repeated measures of a binary response are made for $n_i$ study units in $i$ subpopulations ($i = 1, \ldots, s$), resulting in $r = 2^d$ possible response profiles. Let $\mathbf{p}_i$ denote an $r \times 1$ vector of observed response proportions. Then $n_i \mathbf{p}_i$ will follow a multinomial distribution with parameter $\boldsymbol{\pi}_i$. Linear models are specified for a column concatenation of $u_i$ ($u_i < r$) differentiable functions of $\mathbf{p}_i$, $\mathbf{F}_i = \mathbf{f}_i(\mathbf{p}_i)$, where $\mathbf{F} = (\mathbf{F}'_1 \ \mathbf{F}'_2 \ldots \mathbf{F}'_s)'$ such that $\mathbf{F} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$. Here, $\mathbf{X}$ is a full-rank design matrix, $\boldsymbol{\beta}$ is an unknown parameter vector, and $\boldsymbol{\varepsilon}$ is a $u \times 1$ vector of errors, such that $u = \sum_{i=1}^{s} u_i$.

Parameters are estimated using weighted least squares, where the weights are given by $\mathbf{V}_{\mathbf{F}}^{-1} = \{\mathbf{H}[\mathbf{V}(\mathbf{p})]\mathbf{H}'\}^{-1}$ and $\mathbf{H} = [\partial\mathbf{F}(\mathbf{x})/\partial\mathbf{x} \mid \mathbf{x} = \mathbf{p}]$ is a $u \times sr$ matrix of first partial derivatives of the functions $\mathbf{F}$ evaluated at $\mathbf{p}$. Here

$$\mathbf{V}_i(\mathbf{p}_i) = \frac{1}{n_i}(\mathbf{D}_{\mathbf{p}_i} - \mathbf{p}_i\mathbf{p}'_i), \quad i = 1, \ldots, s$$

and $\mathbf{D}_{\mathbf{p}_i}$ is an $r \times r$ diagonal matrix with elements of $\mathbf{p}_i$ on the main diagonal. Hypotheses of the form $\mathbf{C}\boldsymbol{\beta} = \mathbf{0}$ are tested using Wald statistics.

Applications of the WLS methodology have been made to repeated-measures crossover designs, split-plot designs, and dose–response studies (Stanish and Koch, 1984). Of particular interest to growth applications are settings where the $d$ repeated measures correspond to measures at times $t_0, t_1, \ldots, t_T$ ($T \geq 1$) under each of $M$ conditions such that $d = M(T + 1)$. Models are frequently specified in terms of $q$ ($<T$) polynomial trends over time, where the design matrix for trends in the $i$th subpopulation under the $m$th condition is given as

$$\mathbf{N}_{im} = \begin{bmatrix} 1 & t_0 & t_0^2 & \cdots & t_0^q \\ 1 & t_1 & t_1^2 & \cdots & t_1^q \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ 1 & t_T & t_T^2 & \cdots & t_T^q \end{bmatrix}$$

for $i = 1, \ldots, s$ and $m = 1, \ldots, M$.