Self Modeling with Random Shift and Scale Parameters and a Free-knot Spline Shape Function[*] [†]

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Abstract

The shape invariant model is a semi-parametric approach to estimating a functional relationship from clustered data (multiple observations on each of a number of individuals). The common response curve shape over individuals is estimated by adjusting for individual scaling differences while pooling shape information. In practice, the common response curve is restricted to some flexible family of functions. This paper introduces the use of a free-knot spline shape function and reduces the number of parameters in the shape invariant model by assuming a random distribution on the parameters that control the individual scaling of the shape function. New graphical diagnostics are presented, parameter identifiability and estimation are discussed, and an example is presented.

1   Introduction

In many studies the response of interest is continuous rather than discrete, for instance, a dose or time response curve. The data from such studies usually consist of a number of observations (at different doses, times, locations, etc.) on each of a number of individuals or clusters. Data of this type are called clustered, repeated measures, or, when serial correlation within an cluster is likely, longitudinal data. The outcome of interest may be the shape of the response curve itself or the value of a response feature such as the slope at a particular point or the location of a maximum. Often polynomials or other standard regression model will fit the data. However, in some cases no standard model is appropriate.

An example of this type of data is given in a paper by Lawton, Sylvester and Maggio Lawton *et al.*, 1972. The volume of air expelled by 18 individuals is measured at 20 time points that vary among individuals. A plot of the raw data values with straight lines connecting the observations in each individual's response sequence (Figure 1) indicates a possibly similar shape among the individuals' response curves. The data set, as reported, includes one or two zeros at the beginning of each individuals' data sequence. These values have been omitted from Figure 1 (see Section 5). No specific mechanistic model was postulated for these data and neither polynomials, sums of exponentials, nor the sigmoidal Gompertz growth model fit the individual response sequences well.

Lawton, Sylvester, and Maggio Lawton *et al.*, 1972 propose the self modeling approach for data of this type. Their method is based on the assumption that all individuals' response curves have a common shape and that a particular individual's curve is some simple transformation of the common shape curve. The model which implements this idea is called the shape invariant model. The example given by Lawton, Sylvester, and Maggio Lawton *et al.*,
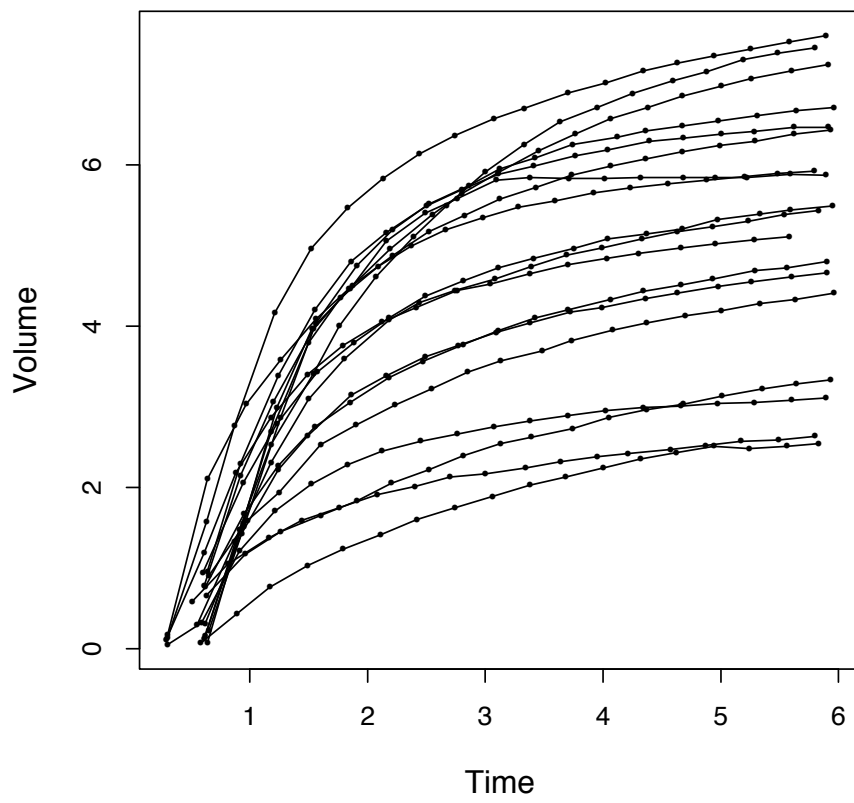
3

Figure 1: Spirometry data. Volume of air expelled versus time for 18 individuals.

1972 expresses the jth observation on the ith individual as

$$y_{ij} = \phi_{i1} + \phi_{i2}\, g\left(\frac{x_{ij} - \phi_{i3}}{\phi_{i4}}\right) + e_{ij} \tag{1}$$

where ϕ_{i1} and ϕ_{i3} are y and x-shift parameters respectively, ϕ_{i2} and ϕ_{i4} are y and x-scale parameters, g is a common shape function, and e_{ij} are independent and identically distributed $\mathcal{N}(0, \sigma^2)$. This is just one possible formation of a shape invariant model. Other, possibly nonlinear, shifting and scaling schemes can be defined but they must be parameterized parsimoniously. A shape invariant model with completely general axis transformations would fit the data perfectly and provide no information.

Even when there is a mechanistic model proposed for a group of response curves, a semi-parametric approach such as self modeling provides an alternate, less model-dependent, analysis and provides a check on modeling assumptions. Self modeling has been applied to a number of data analysis problems including spectrophotometry Lawton and Sylvestre, 1971, spirometry Lawton *et al.*, 1972, pharmacokinetic modeling Verotta and Sheiner, 1992, and the analysis of bioassay and immunoassay dose-response curves Guardabasso *et al.*, 1987; Guardabasso *et al.*, 1988. Estimation and testing of parameters have been discussed by Kneip and Gasser Kneip and Gasser, 1988; Härdle and Marron, 1990.

This paper extends the shape invariant model by incorporating random shift and scale parameters, by choosing the shape function from the free-knot spline family of functions, and by developing new diagnostic graphics. The introduction of random shift and scale effects reduces the number of parameters in the model and improves their identifiability. A mixed effects approach to self modeling also eliminates the need to exclude individuals with too few observations to estimate shift and scale parameters separately. Free-knot splines are flexible shape functions that have the locally determined behavior of nonparametric models but retain a fully parametric structure. They allows simultaneously estimation of the shape function and other model

parameters so that the uncertainty of the shape function is reflected in the variability estimates. New graphical methods are proposed which serve as diagnostic tools and which illustrate the underlying structure of the modeling approach. Estimation for this extended shape invariant model is based on existing methods for nonlinear mixed effects models Lindstrom and Bates, 1990.

The remainder of the paper is organized as follows. Section 2 introduces extensions to the shape invariant model including free-knot spline shape functions, random shift and scale parameters, and improvements in parameter identifiability. Defining and computing estimates and is discussed in Section 3 Section 4 describes a model building strategy and introduces new graphical techniques. An analysis of the spirometry data is presented in Section 5 and Section 6 contains a summary of the paper and describes some extensions to the model.

2   Extending the Shape Invariant Model

A Free-knot Spline Shape Function

Ideally the shape function $g(x)$ should be from a family of flexible approximating function. There are a number of choices available, most of which require the additional assumption of smoothness. Lawton, Sylvester, and Maggio Lawton *et al.*, 1972 implemented a linear fixed-knot spline (a piecewise linear function) and suggested the possible use of cubic splines. Smoothing spline shape functions have been considered elsewhere Guardabasso *et al.*, 1987 and a nonparametric kernel estimator might also fill this role. This paper proposes free-knot regression splines for the shape function because they are flexible, parametric approximating functions with locally determined behavior. Cubic splines are used because they appear smooth to the eye and are sufficiently flexible to approximate most physical response curves with just a few knots.

Fixed and free-knot spline regression are described in detail Reference Eubank, 1988. In brief, a regression spline g on the interval $[a, b]$ with knots $\boldsymbol{\gamma}$, $\boldsymbol{\gamma} = (\gamma_1, \gamma_2, \ldots, \gamma_K)$, $a < \gamma_1 \leq \gamma_2 \leq, \ldots, \leq \gamma_K < b$ is a cubic polynomial between each pair of adjacent knots and in the intervals $[a, \gamma_1]$ and $[\gamma_K, b]$. If the knots are distinct, then the polynomial pieces join so that all derivatives but the third are continuous. We will consider only splines with distinct knots.

We write the b-spline representation of a spline, g, on the interval $[a, b]$ with knots $\boldsymbol{\gamma}$ as

$$g(x, \boldsymbol{\gamma}, \boldsymbol{\alpha}) = \sum_{k=1}^{K+4} \alpha_k \, \mathsf{bspline}_k(x, \boldsymbol{\gamma})$$

where $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_{K+4})^T$ and $\mathsf{bspline}_k$ is the kth b-spline. For notational simplicity, the dependence of some of the b-splines on a and b is implicit. For a fixed knot vector $\boldsymbol{\gamma}$, $g(x, \boldsymbol{\gamma}, \boldsymbol{\alpha})$ is a linear function of the b-spline coefficients $\boldsymbol{\alpha}$. If the knots, as well as the b-spline coefficients, are allowed to vary (free knots), then the spline's flexibility and approximating ability increases de Boor and Rice, 1968. However, the knots enter the spline function nonlinearly and complicate the estimation procedure (see Section 3).

Locally determined function estimates often show erratic behavior at the design boundaries (the endpoints of the smallest closed interval containing all design points) and free-knot splines are no exception. One solution to this problem is to restrict the flexibility of the spline near the design boundaries by extending the spline with linear segments and requiring all but the third derivative to match at the boundaries. This restriction reduces the number of b-spline coefficients by two and the resulting splines are known as natural splines. An alternative approach to controlling unwanted erratic behavior of splines is to restrict the splines to be monotonic or unimodal by imposing restrictions on the b-spline coefficients Ramsay, 1988; Kelly and Rice, 1990. This approach, however, is only appropriate when such restrictions are known *a priori.*

Random shift and scale parameters

A natural extension of the shape invariant model is to assume a mixed effects structure on the scale and shift parameters Lindstrom, 1987. This reduces the number of parameters and allows inclusion of individuals with few observations. A mixed effects shape invariant model has the form:

$$y_{ij} = (\beta_1 + b_{i1}) + (\beta_2 + b_{i2}) \; g \left(\frac{x_{ij} - (\beta_3 + b_{i3})}{(\beta_4 + b_{i4})} \right) + e_{ij}, \qquad \boldsymbol{b}_i \sim \mathcal{N}(\boldsymbol{0}, \sigma^2 \boldsymbol{D}) \;\; (2)$$

where g is a common shape function, $e_{ij} \sim \mathcal{N}(0, \sigma^2)$, $\boldsymbol{b}_i = (b_{i1}, b_{i2}, b_{i3}, b_{i4})^T$, $\sigma^2 \boldsymbol{D}$ is an unstructured variance/covariance matrix, and $\text{cov}(b_{ik}, e_{ij}) = 0$ for all i, j and k. The dimension of the parameter space for the maximum likelihood estimation problem is reduced from $4 \times$ (the number of individuals) plus the number of parameters in the shape function to 4 fixed shift and scale parameters plus the number of parameters in g plus the 10 unique entries in $\boldsymbol{D}$. This is a substantial reduction if there are more than 10 or so individuals.

Identifiability

The parameters in the shape invariant model given in Equation 1 are often not identifiable. (See Kneip and Gasser Kneip and Gasser, 1988 for a discussion of identifiability for a more general class of models.) For instance, if the family of shape functions is closed under multiplication of the shape function or its argument by -1, then we can cancel out a change of sign in all the y-scale parameters ϕ_{i2} by replacing $g(x)$ with $-g(x)$ and we can offset a change in sign in all the x-scale parameters ϕ_{i4} by replacing $g(x)$ with $g(-x)$. This lack of identifiability can be eliminated by forcing the scale parameters to be positive. This is accomplished by optimizing the y and x-scale parameters in the log scale, that is, replace ϕ_{i2} and ϕ_{i4} with $\exp(\phi_{i2})$ and $\exp(\phi_{i4})$ respectively. Negative x or y-scale parameters may be desirable in cases where the response sometimes increases and sometimes decreases in a symmetric pattern around a vertical or horizontal line. Choice of parameter transformation

will depend on the particular data analysis problem.

The distribution of the random shift and scale parameters in the mixed effects model (Equation 2) is not invariant under reparameterization. Typically however, if restricting the scale parameters to be positive makes sense for a particular example then transformation of these parameters to the log scale will result in more normally distributed random effects. All distributional assumptions should be examined during the model building process.

A second, related identifiability problem for most families of shape functions is the ability to compensate for a multiplicative scaling of the y or x-scale parameters by an inverse scaling of the shape function. For spline shape functions (both natural and standard, fixed and free knots), the parameterization of the model as originally proposed (Equation 1 allows us to offset a constant multiplicative scaling of the y-scale parameters (ϕ_{i2} replaced with $\mu\phi_{i2}$ for all i) with a scaling of the shape function (replace $g(x, \boldsymbol{\gamma}, \boldsymbol{\alpha})$ with $g(x, \boldsymbol{\gamma}, \boldsymbol{\alpha}/\mu)$). Similarly, we can cancel out a scaling of the x-scale parameters (ϕ_{i4} replaced with $\mu\phi_{i4}$) by replacing $g(x, \boldsymbol{\gamma}, \boldsymbol{\alpha})$ with $g(x/\mu, \boldsymbol{\gamma}/\mu, \boldsymbol{\alpha})$.

One strategy to reduce this lack of identifiability is to limit the family of shape functions so that it is not closed under this type of scaling. For instance, one might restrict the shape function to have fixed x and y range. Depending on the type of shape function chosen, enforcing a fixed y range might be feasible. In general, however, fixing the range of the shape function on the x-axis would greatly complicate the estimation process.

The mixed effects shape invariant model with log transformed scale parameters provides a simple method for eliminating this lack of identifiability. If the fixed effects β_2 and β_4 are removed so that

$$y_{ij} = (\beta_1 + b_{i1}) + e^{b_{i2}} \, g\left(\frac{x_{ij} - (\beta_3 + b_{i3})}{e^{b_{i4}}}\right) + e_{ij} \qquad (3)$$

then no multiplicative scaling of $e^{b_{i2}}$ or $e^{b_{i4}}$ is possible since the random effects are defined to have mean zero. Intuitively it seems that the fixed effects for the y and x-shift parameters should also be redundant. In fact,

9

the fixed y-shift parameter β_1 is only redundant if there are no random y-scale parameters in the model and if the family of shape functions is closed under addition of a scaler $(g(x) + \mu)$. Likewise, the fixed x-shift parameter β_3 is only redundant if there are no random x-scale parameters and if the family of shape functions is closed under addition of a scaler to the argument $(g(x + \mu))$. This is best seen by rewriting the model in Equation 3 as:

$$y_{ij} = b_{i1} + e^{b_{i2}} \left[\frac{\beta_1}{e^{b_{i2}}} + g\left(\frac{x_{ij} - b_{i3}}{e^{b_{i4}}} - \frac{\beta_3}{e^{b_{i4}}} \right) \right] + e_{ij}$$

While β_1 and β_3 are not mathematically redundant, in practice it is unusual for them to contribute significantly to the model and are often removed during the model building process.

Conclusions about the redundancy of parameters are heavily dependent on the formulation of the model. If we change the parameterization to

$$y_{ij} = e^{(\beta_2 + b_{i2})}((\beta_1 + b_{i1}) + g((\beta_3 + b_{i3}) + e^{(\beta_4 + b_{i4})}x_{ij})) + e_{ij}$$

then, if the family of shape functions is closed under addition of a constant to the function $(\mu + g(x))$, or it's argument $(g(\mu + x))$, the fixed shift parameters, β_1 and β_3 are redundant but the fixed scale parameters, β_2 and β_4 are not.

3 Defining and Calculating Estimates

Estimation

The shape invariant model with a cubic, free-knot, natural spline shape function, random scale and shift parameters, and parameter transformations and reductions as described above, has the form

$$y_{ij} = (\beta_1 + b_{i1}) + e^{b_{i2}} \, g\left(\frac{x_{ij} - (\beta_3 + b_{i3})}{e^{b_{i4}}}, \boldsymbol{\gamma}, \boldsymbol{\alpha} \right) + e_{ij} \tag{4}$$

where

$$g(x, \boldsymbol{\gamma}, \boldsymbol{\alpha}) = \sum_{k=1}^{K+2} \alpha_k \, \mathsf{bspline}_k^N(x, \boldsymbol{\gamma})$$

and where $\mathsf{bspline}_k^N$ is the kth basis function for the space of natural cubic splines Kooperberg and Stone, 1991. This is a nonlinear, mixed effects model with fixed parameters $\boldsymbol{\gamma}$ (knots), $\boldsymbol{\alpha}$ (b-spline coefficients), β_1 and β_2 (fixed shift parameters); random effects $\boldsymbol{b}_i$ (scale and shift parameters); and variance components $\boldsymbol{D}$ and σ. Both fixed and random effects enter the expectation function nonlinearly.

A number of methods have been proposed for parameter estimation in nonlinear mixed effects models. We will use the approximate maximum likelihood approach Lindstrom and Bates, 1990 which has recently been shown to be very accurate Pinheiro and Bates, 1995. In brief, we obtain approximate maximum likelihood estimates for the fixed effects and variance components by first approximating the marginal density of the fixed effects near the mode of the posterior distribution of the random effects with a multivariate normal density and then maximizing the corresponding approximate likelihood. The commonly used estimates for the random effects are the conditional (or shrinkage) estimates.

The consistency of the maximum likelihood estimates for the fixed effects and variance components in linear mixed effects models has recently been established Pinheiro, 1994. In general, these results require that both the number of individuals and the number of unique within individual design points go to infinity. That is, it is not necessary that the number of observations on each individual go to infinity as long as the total number of unique design points relevant to each random effect does. These results have not yet been extended to nonlinear mixed effects models but given the existing consistency results for standard nonlinear models Jennrich, 1969 it is likely that an extension will be possible under similar assumptions.

11

Implementation

Software for fitting shape invariant models was developed in the S statistical language Becker *et al.*, 1988. The two major components are a model function for free-knot natural splines and the nlme function Pinheiro *et al.*, 1993 for nonlinear mixed effects models. Fortran subroutines for natural splines developed by Charles Kooperberg for the logspline density estimation program Kooperberg and Stone, 1991 were used in the model function. The nlme and logspline packages are available from statlib@lib.stat.cmu.edu.

The knot transformation defined by Jupp Jupp, 1978 was used to improved the convergence behavior of the knots. That is, the model function was written in terms of the parameters $\nu_k = \log(h_{k+1}/h_k)$, $k = 1, \ldots, K$, where

$$
h_k = \begin{cases} \gamma_1 - a & k = 1 \\ \gamma_k - \gamma_{k-1} & k = 2, \ldots, K \\ b - \gamma_K & k = K + 1 \end{cases}
$$

This transformation produces parameters $\boldsymbol{\nu}$ that uniquely define the locations of the knots and are neither constrained nor redundant. The Jupp transformation improves, but does not eliminate, the convergence difficulties associated with free-knot splines. The behavior of the optimization routine is further improved by exploiting the conditional linearity of the b-spline parameters Jupp, 1978; Lindstrom and Bates, 1988.

Some minor modifications to nlme were required to accommodate a natural spline shape function. The definition of the basis functions for standard splines requires that end-knots be placed at or outside the design boundaries. For natural splines these end-knots must be placed exactly at the design boundaries or the desirable boundary behavior is lost. This creates complications when estimating the parameters in the shape invariant model. The locations of the end-knots are dependent on fixed and random effects from all individuals since it is the maximum range of $x'_{ij} = (x_{ij} - (\beta_3 + b_{i3}))/b_{i4}$ over all i which defines the relevant design boundaries. One solution is to take into account the dependence of the end-knot locations on the parameters

when optimizing the likelihood. While this would provide more information at each iteration and thus speed up convergence, the loose coupling structure of the nonlinear mixed effects model Soo and Bates, 1992 would be destroyed. Loose coupling requires that the derivative of each individual's expectation with respect to the every other individual's random effects is equal to zero. Taking advantage of loose coupling adds considerable speed to parameter estimation. To maintain this structure we only update the locations of the end-knots between nlme iterations. In practice, this seems to be an appropriate compromise. The nlme function is also modified to take advantage of the conditional linearity of the b-spline coefficients. They are reset to their current least squares estimate after each nlme iteration. This modification improves convergence substantially.

4 Model Building

Mixed effects models

An effective strategy for fitting mixed effects models is to begin by specifying a fixed effects model that is general enough to represent the typical individual response profile. If this model is nonlinear in its parameters, starting values for the fixed effects for subsequent mixed effects model fits can be obtained by fitting the fixed effect model to the data from a representative individual. (If the model is linear no starting values are required for the fixed effects.)

The next step is to add random effects corresponding to each fixed effect and fit this mixed effects model to the entire data set. If there are multiple treatment groups then fixed effects modeling the effect of group are also added at this stage (See Pinheiro *et al.*, 1993 for details). As in all nonlinear regression, failure to converge often indicates over-parameterization of the model. If the complete model cannot be fit, the largest model which successfully converges should be used as the starting model. If the model has been reduced to obtain convergence, it may be possible to obtain convergence for

larger models by using parameter estimates from the reduced model as starting values. After the largest possible model has been fit, the model building process involves removing random effects (individually and in groups) using the Akaike information criterion (AIC) Sakamoto *et al.*, 1986 to check for their importance. While the random effects are being tested for inclusion in the model it may become apparent that certain of the fixed effects are not contributing to the fit. In general, caution should be exercised when removing fixed effects while their corresponding random effects remain in the model.

Once an acceptable model has been found, conditional residuals should be checked for lack of fit keeping in mind that these residuals may exhibit strong correlation within individual but should not display consistent patterns over individuals. Plots of the estimated random effects should be checked for significant deviation from normality.

Shape invariant models

The approach to fitting mixed effects models outlined above is appropriate for the shape invariant model with random effects. An extra concern is the choice of the number of and starting values for the knots. Wold Wold, 1974 gives some rules of thumb for knot placement in cubic splines which may be helpful in choosing starting knots: (1) keep the number of knots to a minimum, (2) a maximum of one extremum and one inflection point between knots, (3) center extreme points in intervals, and (4) place knots close to inflection points. The first rule is particularly important since successful convergence is unlikely if too many knots are specified. The lower the signal to noise ratio in the data, the more knots may be required for a good fit. Starting values for the fixed shift parameters β_1 and β_2 are usually set to some small number, linear least squares provides starting values for the spline coefficients $\boldsymbol{\alpha}$, and the random effects are usually set to zero.

Once the number of knots and starting values are chosen, the next step is to fit the complete shape invariant model given in Equation 4. If convergence

is not obtained then different starting values can be tried and/or one or both of the fixed shift parameters can be removed from the model. This is one situation where it is often necessary to remove a fixed effect while a corresponding random effect remains in the model. It may be appropriate to reduce or increase the number of knots at this point. A variety of starting values for the knot locations should be tried to improve the chances that a global optimum has been found.

If the model building process does not result in a satisfactory fit, potential explanations include: inappropriate axes transformation, serially correlated data, and violation of the assumption that the response sequences can be simply transformed to lie along a common curve. The model can be adjusted to accommodate all but the last of these difficulties.

Diagnostic plots for self modeling

The shape invariant model assumes that we can shift and stretch (or squeeze) the x and y axes separately in a linear fashion for each individual until the data from all the individuals lie approximately on one curve. If we rewrite the model in Equation 1 as:

$$(y_{ij} - \phi_{i1})/\phi_{i2} = g((x_{ij} - \phi_{i3})/\phi_{i4}) + e_{ij}/\phi_{i2}$$

and define

$$y'_{ij} = (y_{ij} - \phi_{i1})/\phi_{i2} \text{ and } x'_{ij} = (x_{ij} - \phi_{i3})/\phi_{i4}$$

then, if the model fits the data, a plot of y' versus x' for all individuals will lie approximately along a single curve indicative of the shape function g. Figure 2 shows the spirometry data plotted in this way. This aggregate scaled data plot is a useful diagnostic tool for assessing the validity of the assumption of common shape function across individuals.

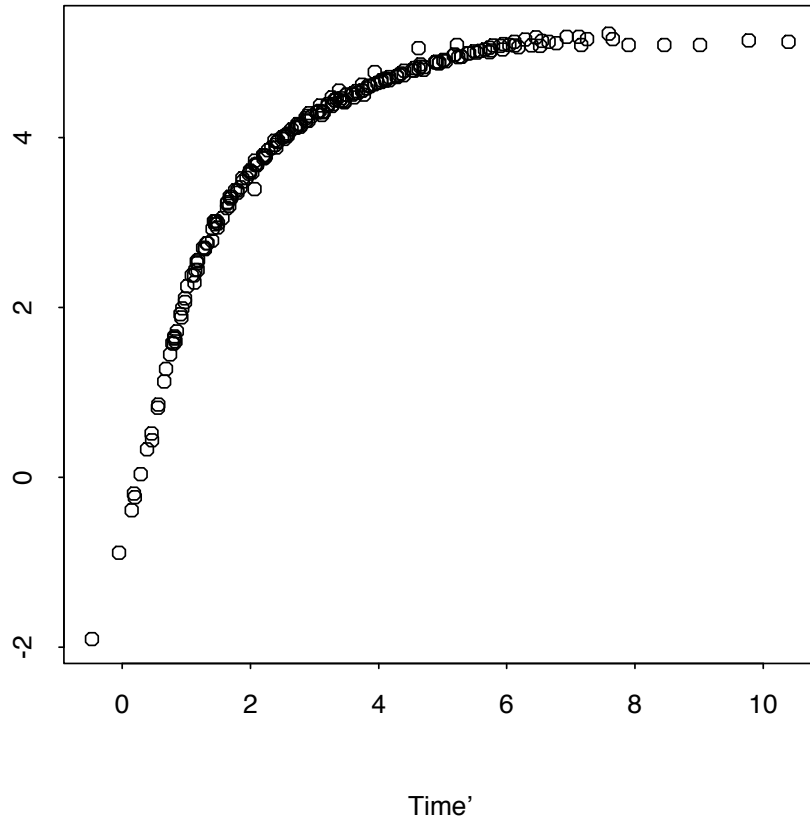Individual scaled data plots with fitted curves (Figure 3) combined with

Figure 2: Shifted and scaled spirometry data. $\mathrm{Volume}'_{ij} = (\mathrm{Volume}_{ij} - \hat{\phi}_{i1})/\hat{\phi}_{i2}$ and $\mathrm{Time}'_{ij} = (\mathrm{Time}_{ij} - \hat{\phi}_{i3})/\hat{\phi}_{i4}$ where i indexes individual and j indexes observations within individual.

16

individual plots of the fitted curves in the original scale (Figure 4) illustrates the shifting and scaling required to fit the common shape curve to each individual. These scaled data plots provide a simple pictorial summary of the structure of the model and are appropriate for all shape invariant models regardless of axis scaling, shape function, or parameter transformation. (Estimates required to construct these plots are given in Section 5.)

5 Spirometry example

The spirometry data were fit using the approach outlined above. The initial points with zero volume in each of the response sequences were removed from the analysis since they introduce a sharp corner in the response and are likely observed before exhalation begins. A three knot, free-knot spline was chosen as a starting point with the starting values for the knots set to $(.5, 1, 3)$. However, the full model (all shift and scale parameters random, both fixed shift parameters included) did not converge. A model with the fixed shift parameters and the y-shift random effect removed did converge successfully with an AIC of -1128. The converged parameters from this fit were used as starting values for a fit with all shift and scale parameters random and an AIC of -1229 was achieved. Plots of the conditional residuals indicated lack of fit so additional knots were added one at a time until the addition of a 7th knot failed to decrease the AIC. The best 6 knot fit had an AIC of -1259 and was a significant improvement over the best 5 knot fit with an AIC of -1256. The conditional residuals showed no lack of fit and the estimated random effects appear more or less normally distributed. Removing each of the random effects in turn from the best 6 knot fit increased the AIC to -1076 or more. The x and y-shift fixed effects were also tested for inclusion in the model but in each case the AIC did not decrease. The final model is:

$$y_{ij} = b_{i1} + e^{b_{i2}} \, g\left(\frac{x_{ij} - b_{i3}}{e^{b_{i4}}}, \boldsymbol{\gamma}, \boldsymbol{\alpha}\right) + e_{ij}, \quad \boldsymbol{b}_i = (b_{i1}, b_{i2}, b_{i3}, b_{i4})^T \sim \mathcal{N}\left(\boldsymbol{0}, \sigma^2 \boldsymbol{D}\right)$$

17
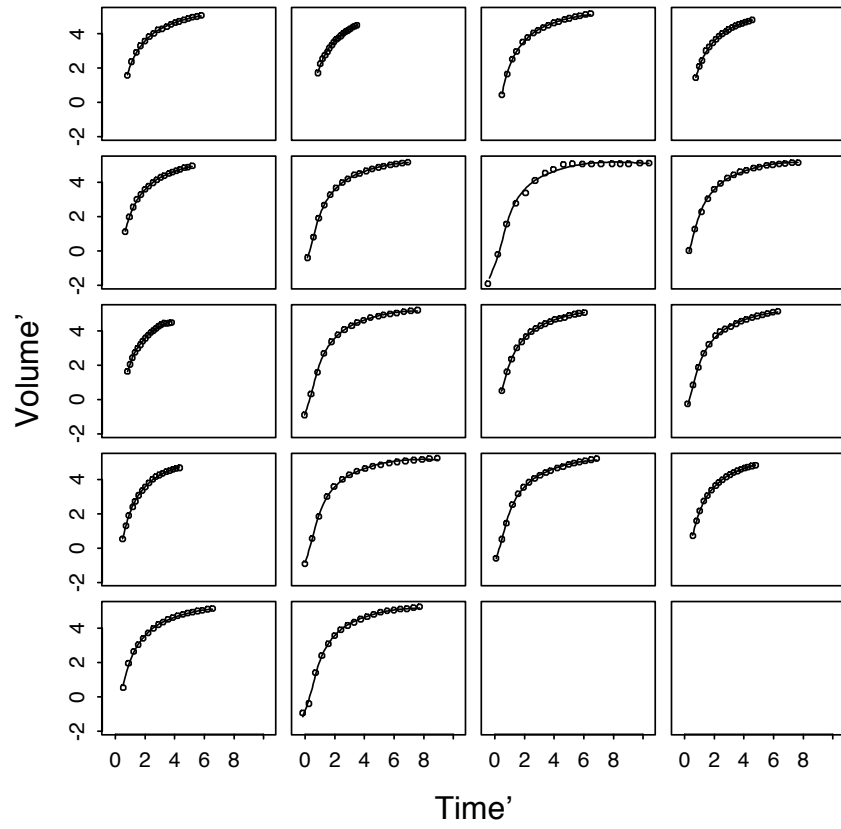
Figure 3: Scaled and shifted spirometry data with individual fitted curves, $g(\text{Time}', \hat{\boldsymbol{\gamma}}, \hat{\boldsymbol{\alpha}})$. See Figure 2 legend for definitions.
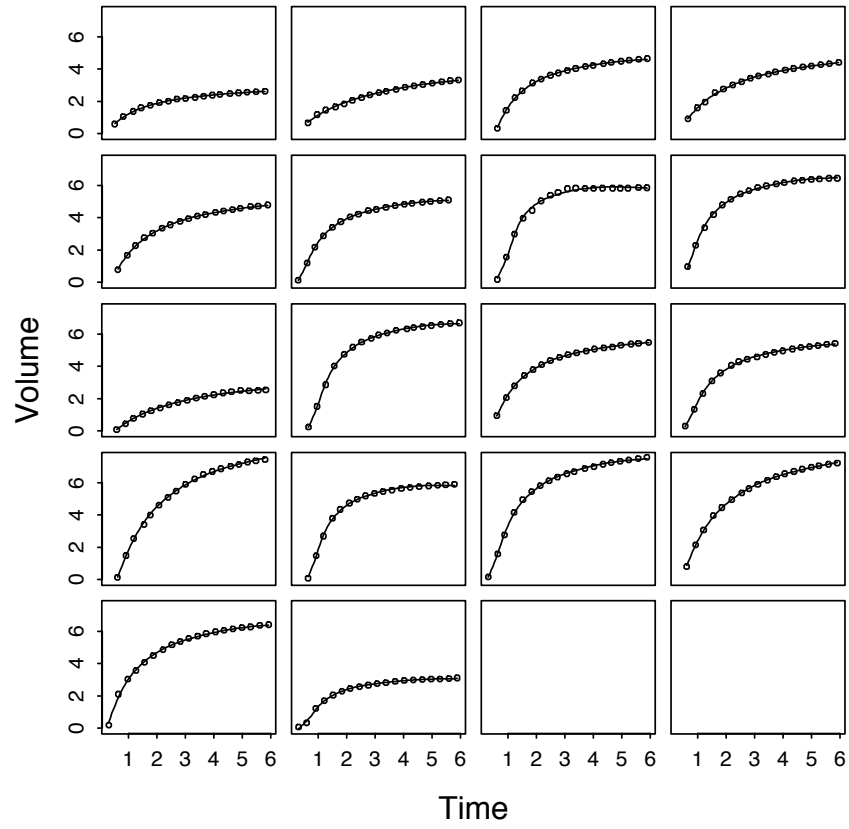
Figure 4: Spirometry data with individual fitted curves.

where g is a cubic natural spline with 6 free knots. This final fit took approximately 20 minutes of clock time for 17 nlme iterations using a Sun Sparcstation 10/51 with 32 megabyte RAM. The approximate maximum likelihood estimates are:

$$\hat{\boldsymbol{\gamma}} = (0.566, 0.621, 1.80, 2.31, 3.59, 4.97),$$

$$\hat{\boldsymbol{\alpha}} = (-0.317, -0.609, 1.038, 29.924, 0.747, 1.7, 0.204, -0.002)$$

$$\hat{\sigma} = 0.00191, \quad \hat{\sigma}^2\hat{\boldsymbol{D}} = \begin{bmatrix} 1.43 & -0.150 & 0.585 & -0.311 \\ -0.390 & 0.103 & -0.045 & 0.036 \\ 0.902 & -0.257 & 0.293 & -0.167 \\ -0.732 & 0.320 & -0.868 & 0.126 \end{bmatrix}$$

where the correlations are listed below the main diagonal in $\hat{\sigma}^2\hat{\boldsymbol{D}}$. Some of the same information contained in these variances and covariances is shown graphically in Figure 5, a pair-wise plot of the conditional estimates of the random effects. The raw data and fitted curve for each individual are displayed in Figure 4.

The y-shift random effect has the largest estimated variance. This parameter was left out of the shape invariant model fit by Lawton, Sylvester and Maggio Lawton *et al.*, 1972 because the baseline appears to be zero for all individuals. This interpretation of the role of the y-shift parameters is too limiting. As can be seen in Figures 3 and 4, combinations of non-zero values of y-scale and x-scale allows any portion of the common shape function to fit an individuals response while still predicting approximately zero response at time zero. The positive correlation between the x and y-shift random effects is consistent with this observation. The x-scale random effect is inversely correlated with the x and y-shift random effects indicating that if an individual starts their exhalation a ways up the common shape curve then some squeezing of the x axis is required. The y-scale random effect is also negatively correlated with the shift parameters but to a lesser extent.

Traditional mixed effects models, including polynomials, sums of exponentials, and the Gompertz growth model, were fit to this data for compar-
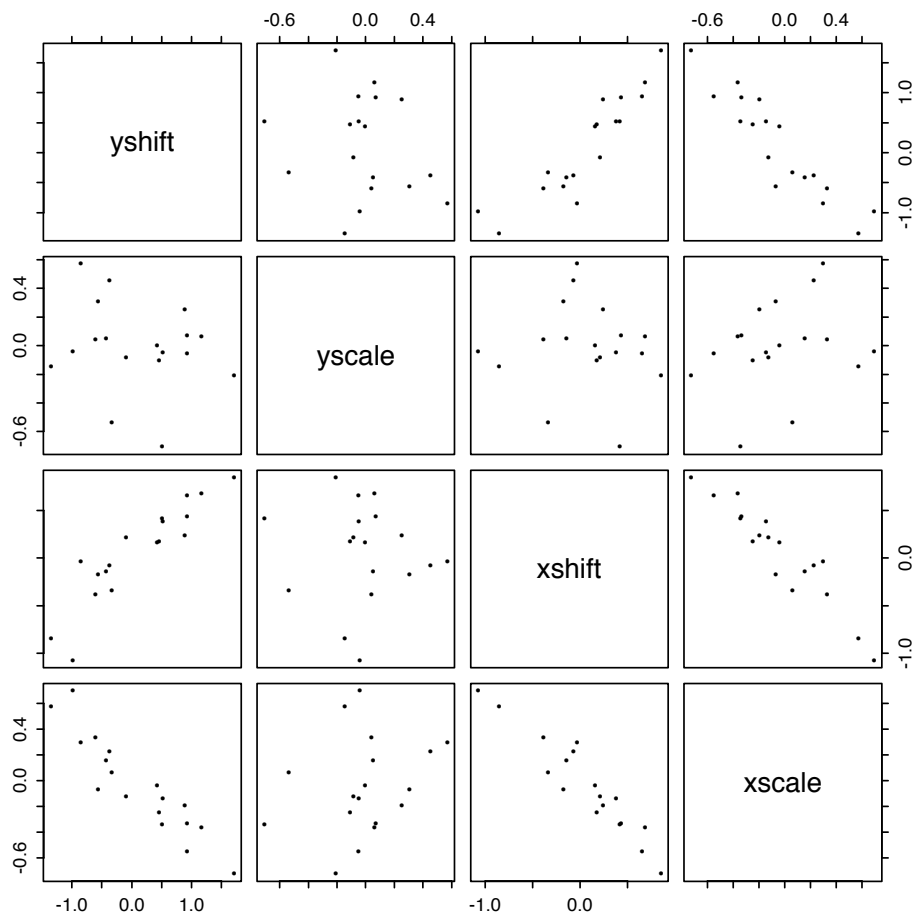
20

Figure 5: Pairwise plots of conditional estimates of random effects.

ison purposes. The best fit was obtained with a double exponential (two compartment) model with with a x-shift parameter: $\alpha(1 - \exp(-k_1(x - \delta)) - \exp(-k_2(x - \delta)))$ where α, k_1 and δ are random over individuals. The AIC for this model (-829) was considerably larger than that of the best shape invariant fit (-1256).

6 Discussion

Summary

This paper extends the shape invariant model proposed by Lawton, Sylvestre and Maggio Lawton *et al.*, 1972 by including random shape and scale parameters and a free-knot spline shape function and by defining new graphical tools. The introduction of random effects reduces the number of parameters (from 86 to 24 in the spirometry example) and improves their identifiability. The mixed effects model formulation allows inclusion of individuals that have insufficient data to estimate the shift and scale parameters separately.

The free-knot spline shape function is flexible, locally determined, and completely parametric. Simultaneous estimation of all parameters ensures that the uncertainty of the shape function is correctly reflected in the variance of the other parameter estimates. Two new plots display the data and fitted model in the x', y' scale. The aggregate scaled data plot (Figure 2) is a diagnostic tool for the assumption that all the scaled and shifted response vectors fall approximately along a single curve. The individual scaled data plot with fitted curves (Figure 3) combined with the fitted curves in the original scale (Figure 4) illustrates how each individuals' data are shifted and scaled to lie along the common curve.

Estimation for the modified shape invariant model was successfully implemented using modified estimation methods and software for nonlinear mixed effects models Lindstrom and Bates, 1990.

22

Extensions

We can extend the shape invariant model to include multiple predictor variables through a number of mechanisms. These include adding completely parametric functions of additional predictors to the model, adding additional terms with different shape functions for each new predictor variable, or using a general shape function of more than one predictor. The first option is fairly simple to implement and would pose no unusual computational problems. The second option is also computationally feasible and creates a model that has similarities to generalized additive models Hastie and Tibshirani, 1986 but with a mixed effects structure. The third option, while theoretically feasible, would require extensive data. One would have to balance the additional data collection required against the need for a completely general function of multiple variables.

The shape invariant model is also easily extended to model changes in the response curves due to different groups or treatments. If two groups appear to have the same shape function, but with different shift or scale parameters, then we can add one or more fixed parameters that shift and/or scale the shape function uniformly for all individuals in the second group. If the two groups appear to require completely different shape functions, then we can add a second shape function for the second group. We might then test this model against one with common shape functions for the two groups or against one with the shape function shifted and scaled for the second group.

The analysis of the spirometry data presented here does not directly model the probably conditional serial correlation. The shape invariant model can be extended to include a parameterized within individual covariance matrix Lindstrom and Bates, 1990 however it is often difficult to differentiate between within individual serial correlation and random effects. This issue requires further study.

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