SMOOTHING SPLINE GROWTH CURVES
WITH COVARIATES

Kurt S. Riedel and Kaya Imre*

Courant Institute of Mathematical Sciences
New York University
251 Mercer St.
New York, NY 10012

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ABSTRACT

We adapt the interactive spline model of Wahba to growth curves with covariates. The smoothing spline formulation permits a nonparametric representation of the growth curves. In the limit when the discretization error is small relative to the estimation error, the resulting growth curve estimates often depend only weakly on the number and locations of the knots. The smoothness parameter is determined from the data by minimizing an empirical estimate of the expected error. We show that the risk estimate of Craven and Wahba is a weighted goodness of fit estimate. A modified loss estimate is given, where $\sigma^2$ is replaced by its unbiased estimate.

*Permanent address: College of Staten Island, C.U.N.Y., Staten Island

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I. INTRODUCTION

Growth curve analysis is used to parameterize a family of temporal curves whose shapes depend on a vector of covariates $\vec{u}$ (Potthoff and Roy (1964), Grizzle and Allen (1969), Geisser (1980)). As an example, we consider the heights of children as a function of time or age and of a number of covariates; both discrete covariates such as sex, and continuous covariates such as drug dosages. We are primarily interested in the case where each individual has been measured a large number of times, so that the growth as a function of time may be treated nonparametrically. We assume that the number of individuals is small enough, or the covariate dependencies are simple enough, that the covariate dependencies may be treated parametrically for each fixed time.

The general theory of growth curves allows arbitrary basis functions and Bayesian priors (Lee and Geisser (1972), Rao (1975), Strenio et al. (1983)). In practice, however, the basis functions are usually assumed to be polynomials in time. Similarly, the covariance matrix of the Bayesian prior is usually a diagonal matrix, or is determined empirically from repeated measurements, or is given a low order autoregressive structure. Smoothing splines is a powerful technique used to reconstruct nonparametric curves and surfaces (see Silverman (1985), Eubank (1988), Muller (1988), Wahba (1990) for reviews). The smoothness penalty function corresponds to a Bayesian prior. Recently, Wahba has developed a general theory of interactive smoothing spline models (Ch. 10, Wahba (1990)). In this brief article, we adapt interactive spline models to growth curve analysis. Our nonparametric growth curve models may also be viewed as a variant of the II model of Breiman (1991) which is appropriate when only one of the covariates is “timelike” and therefore needs to be treated nonparametrically.
Smoothing techniques are widely used for the nonparametric determination of a single growth curve, including the case of repeated measurements (Gasser et al. (1984)). For families of covariate growth curves, however, there has been surprisingly little nonparametric work. Partial linear models (Rice (1986), Heckman (1986), Speckman (1988)) consider growth curves where the parametric part of the model depends on covariates, but the nonparametric part depends only on time: \( \mu(t, \vec{\xi}, i) = \vec{\xi} \cdot \vec{\beta} + f(t) \). Raz (1989) considers families of grouped growth curves, and uses smoothing splines to determine both the individual growth curves and the main effect growth curves. Due to the repeated measurement structure of his model, he is able to determine each nonparametric function separately. A multidimensional nonparametric ANOVA decomposition is given in Gu and Wahba (1991).

Of the two main smoothing techniques, kernel smoothing and smoothing splines, we concentrate on smoothing splines because they generalize more naturally to growth curves with covariates. Despite its generality, we are unaware of any growth curve analysis where the nonparametric part of the model depends on covariates through the standard sum of products structure. Similarly, except our own research (Kardaun et al. (1988), McCarthy et al. (1991), Riedel (1992)), we are unaware of any growth curve analysis with the sum of products covariate structure where the basis representations are regression splines.

We briefly review smoothing splines for a single growth curve with \( n \) independent measurements: \( y_i = f_o(t) + \epsilon_i \) where \( \epsilon_i \sim N(0, \sigma^2) \). We represent the curve as a sum of cubic spline basis functions: \( f_o(t) = \sum_{k=1}^{K} \alpha_k B_k(t) \). In the cubic spline model, the model is a piecewise cubic polynomial with a discontinuous third derivative at each knot locations. When the knots are in the interior of the domain, the number of free pa-
rameters is equal to the number of knots plus four. The free parameters, $\alpha_k$, are determined by minimizing the functional

$$
\min_{\vec{\alpha}} \sum_{i}^{n} \left( \frac{y_i - f_o(t_i, \vec{\alpha})}{\sigma^2} \right)^2 + \lambda_o \int_{0}^{1} \left( f_o^{(\gamma)}(t, \vec{\alpha}) \right)^2 dt , \quad (1)
$$

where $\gamma$ is a positive integer with $2 \leq \gamma \leq 3$. When the smoothing parameter, $\lambda_o$, is zero or too small, the spline coefficients become ill-conditioned and spurious oscillations develop with a wavelength proportional to twice the the distance between knots (Wegman and Wright (1983)). Two remedies for this ill-conditioning are to decrease the number of basis functions and to increase the smoothness parameter $\lambda_o$. Adjusting the spline representation is usually a very complicated optimization. Therefore researchers have concentrated on finding methods which determine the optimal value of $\lambda_o$ from the data. The smoothness penalty function then shrinks the a priori probability of oscillatory behavior to a small and acceptable level.

For a single function, the minimization of Eq. 1 can be done over an infinite dimensional Sobolev space, and the resulting minimum is a cubic spline function with knots at all the measurement locations. In practice, many fewer knots may be sufficient to represent the unknown function, $f_o(t)$. This class of representations is called hybrid spline models. In the covariate growth curve models of Sec. II, the measurement times are usually nonuniform, and we normally consider hybrid spline models with significantly fewer knots than the total number of distinct measurement times.

When hybrid splines are used, two types of error arise: model error from discretization effects and estimation error. Agarwal and Studden (1980) give bounds on the discretization error. We present generalizations of the standard estimation error formulas in Sec. III. Detailed asymptotic analysis can be found in Cox (1984), Eubank (1988), and Wahba (1990).
When discretization error is small relative to the estimation error, hybrid models are generally appropriate since they reduce the ill-conditioning of the estimate at relatively little cost in terms of the total error. For the profile data of Sec. V, we find that the fitted function depends only weakly on the locations of the knots.

II. SEMIPARAMETRIC GROWTH CURVE MODELS

For covariate growth curves, we consider a family of $N$ individuals with the $i$th individual having measured responses at $n_i$ timepoints, $t_{1,i}, \ldots, t_{n_i,i}$. We assume the covariates are fixed in time for the $i$th individual and denote their value by the $M$ vector, $\vec{u}_i$. We denote the $n_i$ vector of the $i$th measurement times, $(t_{1,i}, \ldots, t_{n_i,i})^t$, by $\vec{t}_i$. We denote the $n_i$ vector of measured responses, $(y_{1,i}, \ldots, y_{n_i,i})^t$, by $\vec{y}_i$ and the vector of true values, $(\mu(t_{1,i}, \vec{u}_i, i), \ldots, \mu(t_{n_i,i}, \vec{u}_i, i))^t$, by $\vec{\mu}_i(\vec{t}_i, \vec{u}_i)$. Although we are primarily interested in data which is grouped by individual, multiple time measurements of each individual are not necessary. Uncorrelated measurements may be treated with $n_i = 1$.

We divide the model for $\mu(t, \vec{u}, i)$ into a parametric part, $h(t, \vec{u}, i)$, and a nonparametric part, $f(t, \vec{u}, i)$. The parametric part of the model is assumed to have a specific known functional form: $h(t, \vec{u}, \vec{\beta}, i) = \sum_{j=1}^{J} h_j(t, \vec{u}, i) \beta_j$, where the $h_j(t, \vec{u}, i)$ are known functions and the $\beta_j$ are undetermined free parameters. We allow both the parametric and nonparametric terms to depend on the specific individual to allow for fixed effects models.

We therefore consider growth curve models of the form

$$\mu(t, \vec{u}, i) = h(t, \vec{u}, \vec{\beta}, i) + f_0(t) + \sum_{t=1}^{L} f_t(t) g_t(\vec{u}, i). \quad (2a)$$

We assume that the temporal structure of the $f_t(t)$ is sufficiently complex that it requires a nonparametric representation. The model of Eq. 2a
is a special case of the II model of Breiman (1991). We assume that
the covariate dependencies, \( g_\ell(\vec{u}, i) \), are either given or that they depend
on a low number of free parameters, \( \vec{\beta} \): \( g_\ell(\vec{u}, i, \vec{\beta}) \). In contrast, Breiman
estimates both \( f_\ell(t) \) and \( g_\ell(\vec{u}, i) \) nonparametrically.

When the last term, \( \sum_{\ell=1}^{L} f_\ell(t)g_\ell(\vec{u}, i) \), is omitted, our models reduce
to the standard partial linear spline models. Our sum of products covariate
spline models resemble generalized additive models, and we expect many of
the same techniques and theorems to apply (Friedman and Stuetzle (1981),
Hastie and Tibshirani (1990), Friedman (1991)). Similar to Wahba’s in-
teractive spline model, we use a separate smoothing spline for each of the
\( f_\ell(t) \).

In most applications, the covariate basis functions, \( g_\ell(\vec{u}) \), are linear,
\( (u_m - \bar{u}_m) \), or quadratic, and are centered about the database mean or
are discrete variables. If the nonparametric part of each individual curve
is considered noise, a nonparametric function may be included for each
separate individual: \( g_\ell(\vec{u}, i) = \delta_{\ell,i} \).

In our initial study of profile variation (Kardaun et al. (1988), Mc-
Carthy et al. (1991)), the data consisted of \( N \) sets of temperature mea-
surements at 15 different radial locations in a fusion plasma, with \( 10 \leq
N \leq 100 \). The radial location, \( r \), is the timelike variable, and the main
covariate is \( q \), which corresponds to the ratio of the average magnetic field
to the total plasma current. The shape of the profiles is much less variable
than the overall magnitude; therefore each individual curve was given its
own own own intercept: \( h_j(t, \vec{u}, i) = \delta_{j,i} \). Thus the log linear nonparametric
model of McCarthy et al. (1991) is

\[
\ln[T(r, q, i)] = \beta + f_0(r) + f_1(r)\ln(q) .
\] (2b)

In our earlier study, we used regression splines (\( \lambda = 0 \)) with only three
knots. In Section V, we consider data with more than 60 measurements per profile. This data requires many more knots, and the resulting estimation problem is ill-conditioned without a smoothness penalty function.

We assume that both the number and choice of both the parametric basis functions, \( h_j(t, \vec{u}, i) \), and the covariate basis functions, \( g_k(\vec{u}, i) \) are given \textit{a priori}. In practice, both sets of basis functions are often determined iteratively using a combination of statistical common sense and the minimizations of weighted sums of residual errors and smoothness/degree of freedom/predictive error penalty functions.

Each of the functions, \( f_\ell(t) \), is given a radial representation: \( f_\ell(t) = \sum_{k=1}^{K} \alpha_{k\ell} B_k(t) \), where the \( B_k(t) \) are basis functions. We recommend the choice of \( B \) splines for the \( B_k \) (deBoor (1978)). \( B \) splines are a particular reparameterization of the standard piecewise polynomial splines which have the advantage that each function is spatially localized. The resulting design matrix has a band structure. In practice, the innermost and outermost basis functions are often restricted to be linear in time.

When the temporal design is uniform, \( \vec{t}_i = \vec{t}_j \), the knot positions may be chosen at all the distinct measurement times. If each individual is measured at slightly different times, \( t_{p,i} = \bar{t}_p + \tilde{t}_{p,i} \), we can choose the knot locations at the typical measurement times, \( \bar{t}_p \). Alternatively, we can place a knot at every distinct measurement time: \( t_{p,i} \). The value of the additional knots in reducing the model error depends on the ratio of the typical time between measurements, \( \bar{t}_{p+1} - \bar{t}_p \), to the the spread of the measurement times, \( \sigma_{tp} \) where \( \sigma_{tp}^2 \equiv \frac{1}{N} \sum_{i=1}^{N} \tilde{t}_{p,i}^2 \). In many cases, the spread of times is small relative to the typical time between measurements. In these cases, we typically choose the first alternative, knot locations only at \( \bar{t}_p \). Alternatively, the number and location of the knot positions can be determined by convergence tests or by the data-based parameter selection
criteria of Sec. III.

We denote the $K \times (L + 1)$ matrix whose elements are $\alpha_{k,\ell}, \ell = 0, \ldots L, k = 1, \ldots K$ by $\alpha$, and the $\ell$th column vector by $\tilde{\alpha}_{\ell}; \tilde{\alpha}_{\ell_k} \equiv \alpha_{k,\ell}$. The $n_i \times K$ temporal design matrix for the nonparametric part of the $i$th individual is denoted by $X_i$ with elements $X_i^p,k = B_k(t_p,i)$. Similarly, the parametric part of the design matrix is defined by $H_i^p,\ell = h_\ell(t_p,i, \vec{u}_i, i)$. Thus the $i$th individual is parameterized by

$$
\vec{\mu}_i(\vec{t}_i, \vec{u}_i) = H_i \vec{\beta} + X_i \alpha \vec{g}(\vec{u}_i, i),
$$

(3)

where $\vec{g}(\vec{u}_i, i) \equiv (1, g_1(\vec{u}_i, i), \ldots g_L(\vec{u}_i, i))^t$, and $\alpha$ is the $K \times (L + 1)$ matrix of unknown parameters. Our construction of the nonparametric design matrix specifically assumes that the covariates, $\vec{u}_i$, are time independent. If the covariates are time dependent, the Kronecker product design structure, $(\vec{g}(\vec{u}_i, i)^t \otimes X_i)$, should be replaced by $X_i^t G p,\ell K + k = B_k(t_p,i)g_\ell(\vec{u}_i(t_p,i), i)$, and $\alpha$ is replaced by $\alpha G$, the concatenation of the columns of $\alpha$.

The error structure is assumed to be independent between individuals, but arbitrary within each individual. The $n_i \times n_i$ covariance matrix, $\Sigma_i$, of the measurement errors may be either given or estimated. Thus our models include random effects models for the nonparametric part.

To determine the free parameter matrix in our smooth spline growth curve model, we minimize over $\alpha, \vec{\beta}$ the functional:

$$
\sum_{i=1}^N (\vec{y}_i - \vec{\mu}_i(\vec{t}_i, \vec{u}_i, \alpha, \vec{\beta}))^t \Sigma_i^{-1}(\vec{y}_i - \vec{\mu}_i(\vec{t}_i, \vec{u}_i, \alpha, \vec{\beta})) + \sum_{\ell=0}^L \lambda_\ell \int |f^{(\gamma)}_\ell(t, \vec{\alpha}_{\ell})|^2 dt
$$

(4)

where $\gamma$ is an integer with $2 \leq \gamma \leq 3$. The second term consists of a separate smoothness penalty function for each of the $f^{(\gamma)}_\ell(t)$. The smoothing parameters, $\lambda_\ell$, control the tradeoff between the goodness-of-fit, $\sum_{i=1}^N (\vec{y}_i - \vec{\mu}_i(\vec{t}_i, \vec{u}_i, \alpha, \vec{\beta}))^t \Sigma_i^{-1}(\vec{y}_i - \vec{\mu}_i(\vec{t}_i, \vec{u}_i, \alpha, \vec{\beta}))$, and the smoothness of the solution. If necessary, the utility functional may be robustified in the standard
ways. Our analysis generalizes to smoothing surfaces with covariates. In
other words, if time, \( t \), is replaced by two nonparametric variables such
as time and age, \((t, s)\), our formulas remain valid if \( f_{\ell''}(t)^2 \) is replaced by
\[ |\partial_t^2 f_{\ell}|^2 + 2|\partial_t \partial_s f_{\ell}|^2 + |\partial_s^2 f_{\ell}|^2. \]

Each penalty function may be represented parametrically as
\[ \alpha_t^k S \alpha_t = \int_0^1 f_{\ell}^{(\gamma)}(t)^2 dt, \]
where \( \alpha_t^k \equiv \int_0^1 B_k^{(\gamma)}(t)B_k^{(\gamma)}(t)dt \). Differentiating Eq. 4 with
respect to \( \alpha_t^k \) yields
\[ \sum_{i=1}^{N} q_t(\tilde{u}_i, i) \left( X_i^T \Sigma_i^{-1} X_i \alpha \tilde{g}(\tilde{u}_i, i) - X_i^T \Sigma_i^{-1} (\tilde{y}_i - H_i \tilde{\beta}) \right) + \lambda_t S \alpha_t = 0. \] (5a)

The corresponding variation of Eq. 4 with respect to \( \beta \), the parametric
part of the model, yields:
\[ \sum_{i=1}^{N} H_i^T \Sigma_i^{-1} H_i \tilde{\beta} = \sum_{i=1}^{N} H_i^T \Sigma_i^{-1} (\tilde{y}_i - X_i \alpha \tilde{g}(\tilde{u}_i, i)) . \] (5b)

This is a linear system of \((L + 1)K + J\) unknowns. The optimal values
of the \((L + 1)\) smoothing parameters, \( \lambda_t \), are unknown and also may
be determined from the data.

We now reformulate Eq. 5 as a generalized ridge regression with
\( K(L + 1) + J \) unknowns and \( N_T \) measurements, where \( N_T \equiv \sum_{i=1}^{N} n_i \).
We concatenate the columns of the \( n \) individual measurements into a \( N_T \)
vector, \( \tilde{Y}_c \), and the columns of \( \alpha \) and \( \beta \) into a \( K(L + 1) + J \) vector \( \tilde{\alpha}_c : \)
\[ \tilde{\alpha}_c \equiv (\alpha_t^1, \alpha_t^2, ..., \alpha_t^L, \beta). \] The \( N_T \times (K(L + 1) + J) \) design matrix consists
of the concatenation of the \( N \) matrices \((\tilde{g}(\tilde{u}_i, i)^T \otimes X_i, H_i)\), or for time
dependent covariates, \((X_{G,i}, H_i)\).

The total covariance matrix, \( \Sigma_c \), consists of diagonal matrix entries,
\( \Sigma_i \). The total penalty function, \( S_c(\tilde{\lambda}) \), consists of diagonal matrix entries
\[ \lambda_\ell S : S_c(\tilde{\lambda})_{\ell K+k, \ell' K+k'} = \lambda_\ell S_{k,k'} \delta_{\ell,\ell'} \text{ for } 0 \leq \ell \leq L \text{ and zero otherwise. In} \]
this formulation, Eq. 5 is transformed to

\[
\left( \mathbf{X}_c^t \Sigma_c^{-1} \mathbf{X}_c + \mathbf{S}_c(\bar{\lambda}) \right) \hat{\alpha}_c(\bar{\lambda}) = \mathbf{X}_c^t \Sigma_c^{-1} \hat{\mathbf{Y}}_c .
\] (6)

Our interactive spline models are a special class of mixed models. As such, the covariance structure may be parametrized with a free parameter vector, \( \theta: \Sigma_c = \Sigma_c(\theta) \), and \( \theta \) may be estimated using a restricted maximum likelihood estimator (Harville (1977)). The Bayesian posterior covariance of the discretized system is

\[
\text{Cov} \left( \hat{\alpha}_c, \hat{\alpha}_c^t \right) \equiv \left( \left( \mathbf{X}_c^t \Sigma_c^{-1} \mathbf{X}_c \right)^{-1} + \mathbf{S}_c(\bar{\lambda})^{-1} \right)^{-1},
\] (7)

where \( \mathbf{S}_c(\bar{\lambda})^{-1} \) is the Moore-Penrose generalized inverse of \( \mathbf{S}_c(\bar{\lambda}) \).

III. DATA-BASED PARAMETER DETERMINATION

The optimal values of the smoothing parameters, \( \bar{\lambda} \), are unknown, and we endeavor to estimate them from the data. Most data-based estimates determine the free parameters by minimizing a functional of the data. Risk-based methods minimize a functional related to the predictive error, appropriately weighted (Hall and Titterington (1987)). Goodness of fit methods minimize the residual squared error weighted by a measure of the number of effective degrees of freedom.

We now present several common goodness of fit functionals, and then a class of risk-based functionals. These functionals do not require the growth curve structure which we discussed previously. Instead, we require only that the covariance structure, \( \Sigma_c \), is known up to an arbitrary scalar: \( \Sigma_c = \sigma^2 \hat{\Sigma} \). We also assume that the penalty matrix, \( \mathbf{S}_c(\bar{\lambda}) \) satisfies \( \mathbf{S}_c(\bar{\lambda}) = \sum \lambda_e \mathbf{S}_e \). We redefine \( \bar{\lambda}: \bar{\lambda}^{\text{new}} \equiv \bar{\lambda}^{\text{old}} \sigma^2 \). We define \( \mathbf{C} \equiv \mathbf{X}_c^t \hat{\Sigma}_c^{-1} \mathbf{X}_c \), and the matrices, \( \mathbf{G}(\bar{\lambda}) \), and the influence matrix,
\[ A_c(\bar{\lambda}) :\]

\[ G(\bar{\lambda}) \equiv \left( X^t \bar{\Sigma}^{-1} X_c + S_c(\bar{\lambda}) \right)^{-1}, \quad A_c(\bar{\lambda}) \equiv X_c G(\bar{\lambda}) X^t \bar{\Sigma}^{-1}. \] (8)

The influence matrix is not a projection due to the penalty matrix, \( S_c(\bar{\lambda}) \):

\[ A_c(\bar{\lambda}) > A_c(\bar{\lambda}) A_c(\bar{\lambda}), \] and therefore the concept of effective degrees of freedom is tenuous.

Most of the goodness of fit data-based functionals (when \( \sigma^2 \) is unknown) are of the form:

\[ V(\bar{\lambda}) \equiv \frac{\| (\bar{Y}_c - A_c(\bar{\lambda}) \bar{Y}_c)^t \bar{\Sigma}^{-1} (\bar{Y}_c - A_c(\bar{\lambda}) \bar{Y}_c) \|^2}{N_T M(A_c(\bar{\lambda}))}, \] (9)

where \( M \) is a real valued function on \( N_T \times N_T \) matrices. Furthermore, these functionals usually satisfy \( M(A_c(\bar{\lambda})) \sim 1.0 - 2 \text{Trace}(A_c(\bar{\lambda}))/N_T \) when \( N_T \gg \text{Trace}(A_c(\bar{\lambda})) \) (Hardle, Hall, and Marron (1988)). Generalized cross-validation (G.C.V.) (Craven and Wahba (1979)) is the most widespread data-based functional of the form given by Eq. 9, with \( M(A_c(\bar{\lambda})) \equiv |1.0 - \text{Trace}(A_c(\bar{\lambda}))/N_T|^2 \). Another goodness of fit functional is the corrected Akaike information criteria (Hurvich and Tsai (1989)), which is based on the information content. G.C.V. automatically includes the effects of model error including discretization error in its estimate of the optimal \( \bar{\lambda} \). In contrast, estimates of the expected error often neglect model error including discretization error.

The total expected error in \( \tilde{\alpha}_c(\bar{\lambda}) \) from the sampling perspective, assuming the discrete model is correct, is

\[ E \left[ (\tilde{\alpha}_c(\bar{\lambda}) - \alpha_c)(\tilde{\alpha}_c(\bar{\lambda}) - \alpha_c)^t \right] = \sigma^2 G(\bar{\lambda}) C G(\bar{\lambda}) + G(\bar{\lambda}) S_c(\bar{\lambda}) \tilde{\alpha}_c \tilde{\alpha}_c^t S_c(\bar{\lambda}) G(\bar{\lambda}). \] (10a)

\( \sigma^2 G(\bar{\lambda}) C G(\bar{\lambda}) \) is the variance, and \( G(\bar{\lambda}) S_c(\bar{\lambda}) \tilde{\alpha}_c \tilde{\alpha}_c^t S_c(\bar{\lambda}) G(\bar{\lambda}) \) is the bias error. For any positive semidefinite matrix, \( Q \), we can select \( \bar{\lambda} \) by minimizing
\[ R(\bar{\lambda}, Q) = \text{Trace}(Q \, E \left[ (\hat{\alpha}_c(\bar{\lambda}) - \bar{\alpha}_c)(\hat{\alpha}_c(\bar{\lambda}) - \bar{\alpha}_c)^t \right]) = \]

\[ \text{Trace}\left( Q \left[ \sigma^2 \mathbf{G}(\bar{\lambda})\mathbf{C} \mathbf{G}(\bar{\lambda}) + \mathbf{G}(\bar{\lambda})\mathbf{S}_c(\bar{\lambda})\bar{\alpha}_c\bar{\alpha}_c^t\mathbf{S}_c(\bar{\lambda})\mathbf{G}(\bar{\lambda}) \right] \right), \quad (10b) \]

with respect to \( \bar{\lambda} \). When \( Q \equiv X^t\Sigma^{-1}X \), the risk estimate corresponds to minimizing the predictive error. Choosing \( Q = S_c \) corresponds to minimizing the average expected square error in estimating the \( \gamma \)th radial derivative. From the asymptotic results of Cox (1984), we expect that derivative estimation will require larger values of \( \lambda \) than estimating the unknown profiles. Equations 9 and 10 are generalizations of previously known functionals (Craven and Wahba (1979)) to an arbitrary covariance matrix, \( \Sigma_c \), and similar equations are given in Diggle and Hutchinson (1989). When \( \bar{\lambda} \) is selected to minimize the risk, we have:

\[ \frac{1}{2} \frac{\partial R(\bar{\lambda}, Q)}{\partial \lambda_\ell} = 0 = \text{Trace} \left[ Q \mathbf{G}(\bar{\lambda})\mathbf{S}_c(\bar{\lambda}) \left( \mathbf{C} \bar{\alpha}_c\bar{\alpha}_c^t\mathbf{S}_c(\bar{\lambda}) - \sigma^2 \mathbf{C} \right) \mathbf{G}(\bar{\lambda}) \right], \quad (11) \]

When \( \sigma^2 \) is known, but \( \bar{\alpha}_c \) is unknown, we have the following estimate for the minimum of the expected loss:

\[ \frac{1}{2} \frac{\partial \hat{R}(\bar{\lambda}, C)}{\partial \lambda_\ell} = 0 = \]

\[ \hat{Y}_c^t\hat{\Sigma}^{-1}X_c\mathbf{G}(\bar{\lambda})\mathbf{S}_c(\bar{\lambda})\mathbf{G}(\bar{\lambda})\mathbf{S}_c(\bar{\lambda})X_c^t\hat{\Sigma}^{-1}\hat{Y}_c - \sigma^2 Tr \left[ \mathbf{G}(\bar{\lambda})\mathbf{S}_c(\bar{\lambda})\mathbf{G}(\bar{\lambda})\mathbf{C} \right], \quad (12) \]

where we have restricted to \( Q = C \). Equation 11 or 12 constitute a set of \( L + 1 \) equations to determine the optimal values of \( \{\lambda_\ell\} \). When \( \Sigma \) is known and the errors are uncorrelated, the risk-based estimate, \( \hat{R}(\bar{\lambda}, C) \) was proposed in Craven and Wahba (1979). We prefer the differential formulation of Eq. 12, \( \frac{1}{2} \frac{\partial \hat{R}(\bar{\lambda}, C)}{\partial \lambda_\ell} = 0 \), because Eq. 12 shows explicitly that minimizing \( \hat{R} \) is a weighted goodness of fit estimator.

In practice, \( \sigma^2 \) is often unknown, and can be estimated from the data
using
\[ \hat{\sigma}^2 = \frac{\| (\bar{Y}_c - \hat{A}_c(0)\bar{Y}_c)\hat{\Sigma}^{-1}(\bar{Y}_c - \hat{A}_c(0)\bar{Y}_c) \|}{[N_T - \text{tr}(\hat{A}_c(0))]}, \tag{13} \]
where \( \hat{A}_c(0) = \hat{X}_C X_t \hat{\Sigma}^{-1} \). The variance in the estimate of \( \sigma^2 \) of Eq. 13 is inversely proportional to \([N_T - \text{tr}(\hat{A}_c(0))]\), and therefore increases as the number of spline basis functions grow. We can choose the number of basis functions to minimize the tradeoff of variance in \( \hat{\sigma}^2 \) to bias in the discretization error.

The number and choice of the basis functions, \( h_j(t, \vec{u}, i) \), and \( g_\ell(\vec{u}) \), may also be determined by minimizing the data-based functional. However, as the dimension of the multivariate minimization increases, these data-based functionals may have a number of relative minima. Furthermore, the minimum of the function is often shallow, and the estimated value of \( \hat{X} \) may converge slowly to its optimal value as \( N \) tends to infinity. The convergence to the optimal value is slow when the utility function, \( V(\lambda) \), is an insensitive function of the smoothing. On the other hand, in these cases, the risk/goodness of fit is not dramatically worsened by the use of a suboptimal value of \( \lambda \).

IV. NUMERICAL IMPLEMENTATION

In our numerical implementation, we concatenate the rows of the \( K \times (L + 1) \) matrix \( \alpha \) instead of the columns. The corresponding \( n_i \times K(L + 1) \) design matrix for the \( i \)th individual satisfies \( X^i_{j, (L+1)(k-1)+\ell+1} = B_k(r^i_j)g_\ell(u_i) \) where \( j = 1 \ldots n_i \). The advantage of this reordering of the unknown coefficients is that the resulting \( X^T X \) matrix has a band structure.

The empirical estimate of the minimizing risk, Eq. 12 can be rewrit-
ten as

$$\lambda_\ell = \frac{\sigma^2 Tr \left[ G(\bar{\lambda})S_\ell G(\bar{\lambda})C \right] - \sum_{\ell' \neq \ell} \lambda_{\ell'} \tilde{\alpha'} \alpha_{\ell'} G(\bar{\lambda})S_{\ell'} \tilde{\alpha} \tilde{\alpha}' S_{\ell'} G(\bar{\lambda})S_{\ell} \tilde{\alpha}}{\tilde{\alpha}' S_{\ell} G(\bar{\lambda})S_{\ell} \tilde{\alpha}} \quad (14a)$$

where \( \tilde{\alpha} \) is given in Eq. 6. We iteratively evaluate Eq. 14a for each \( \lambda_\ell \) to minimize Eq. 12.

Two simplifications of the \( \lambda \) estimate are possible. First, when \( G(\bar{\lambda}) \) is approximately block diagonal, we can neglect the second term in the numerator of Eq. 14a, and the simplified equation is

$$\lambda_\ell = \frac{\sigma^2 Tr \left[ G(\bar{\lambda})S_\ell G(\bar{\lambda})C \right]}{\tilde{\alpha}' S_{\ell} G(\bar{\lambda})S_{\ell} \tilde{\alpha}} \quad (14b)$$

In practice, the variance in the estimated mean profile, \( f_0(t) \), is usually much smaller than the variance in the estimates of \( f_1(t) \ldots f_\ell(t) \). Thus if all \( \lambda_\ell \) are equal, the smoothing tends to be too little for \( f_0(t) \) or too much for \( f_1(t) \ldots f_\ell(t) \). Thus a second simplification is to reduce the dimensionality of the minimization by imposing the model restriction: \( \lambda_1 \equiv \lambda_2 \ldots \lambda_\ell \) and \( \lambda_0 \neq \lambda_1 \).

V. EXAMPLE

We consider a 40 profile dataset from the Tokamak Fusion Test Reactor (T.F.T.R.) at the Princeton Plasma Physics Laboratory (Hiroe et al. (1988)). Each profile consists of approximately 61 temperature measurements at different spatial locations. In contrast, the data from our earlier study of the A.S.D.E.X. tokamak had only 15 spatial locations. Thus the A.S.D.E.X. data was well modeled with a spline with only three knots while the T.F.T.R. data is better suited to a smoothing spline ten or more knots.

In the middle of the plasma, the error bars are proportional to the temperature, while the errors at boundary are roughly constant. Thus
we use the logarithm of the temperature as the dependent variable and increase \( \Sigma_{k,k} \) towards the boundary. We estimate \( \sigma^2 \) by fitting each profile separately to a one dimensional model. We use \( \gamma = 3 \) in the penalty function. To determine \( \lambda_0 \) and \( \lambda_1 \), we iterate Eqs. 6 & 14b.

Figure 1 plots the raw data and the fitted profile for the two profiles with the largest and smallest value of \( q \) for the fourteen knot fit. Figure 2 gives the corresponding fit with 46 knots. The similarity of the two fits supports our assertion that smoothing spline fits are often only weakly dependent on the choice of knots. Similarly, the fits are also insensitive to the values of \( \lambda_0 \) and \( \lambda_1 \). The error bars in Figs. 1 & 2 are given by the “plug-in” approximation, i.e. we substitute \( \hat{\alpha} \) into Eq. 10a to estimate the local value of the expected square error for the profiles fits. The expected error increases near the boundaries, partly because the measurement variance increases near the boundary. To reduce the boundary effect, we have increased the spacing between knots near the boundary. The vertical lines on Figs. 1 & 2 give the knot locations.

We have fit the profiles with up to four covariates, plasma \( q \), average particle density, average magnetic field, and electrical voltage. The additional covariates do not produce any noticeable change in the predicted profiles.

The slight misfits near \( r = 2 \) for the low \( q \) profile and near \( r = 2.5 \) for the high \( q \) profile appear to be due to random variation in the profile shape rather than systematic errors in the additive spline model. For a given profile, the residual errors tend to be uniformly positive or negative, indicating that the shape of the temperature profile is better determined than the magnitude of the average temperature. We are currently implementing the random intercept covariance model: \( \Sigma_{j,k} = \sigma^2 \delta_{j,k} + \sigma_o^2 \). The model of Eq. 2b is the corresponding fixed effects model for the intercept.
For a more detailed discussion of the experimental findings, we refer the reader to (Imre and Riedel (1993)).

VI. SUMMARY

Growth curves characteristically have much temporal structure and resolution and relatively poorly resolved covariate structure. Thus we apply nonparametric smoothing splines in the temporal representation and simple, parametric representations in the covariate directions. This class of models does not require multiple time measurements, but the class is well suited to this structure. In other situations, there may be only enough data in the temporal direction for parametric representations or sufficient data in the covariate directions for a nonparametric representation.

We close by noting that Eq. 12 is the general matrix weighting of the residual error that estimates the value of $\lambda$ which minimizes the expected loss. Under the assumption that $C$ and $S$ are equal up to a scalar multiple, Hall & Titterington (1987) have shown that estimating minimizer of the expected loss is equivalent to a specific goodness of fit estimator. Equation 12 generalizes the Hall & Titterington result to the case when $C \neq cS$.

APPENDIX: UNIFORM TEMPORAL DESIGN

When the temporal design is uniform, i.e. $X_1 = X_2 \ldots = X_N$, Eq. 5a may be recast in multivariate form. For simplicity, we assume $\tilde{\beta} \equiv 0$ in this appendix. The $N$ observed profiles, each consisting of the same $n$ time points, can be represented by a $n \times N$ data matrix, $Y$. The $(L + 1) \times N$ covariate data matrix, $U$, has columns $\vec{g}(\vec{u}_1)$ through $\vec{g}(\vec{u}_N)$. In multivariate notation, the growth curve model is

$$Y = X\alpha U + E,$$

(15)
where $E$ is the $n \times N$ matrix of random errors. The first variation of the utility functional (Eq. 5a) can be rewritten as

$$
(X'\Sigma^{-1}X\alpha U^t + S\alpha \Lambda) = X'\Sigma^{-1}Y U^t,
$$

(16)

where $\Lambda$ is a $(L + 1) \times (L + 1)$ diagonal matrix whose elements are $\lambda_\ell$. Unfortunately, the tensor product formulation does not allow a solution based on the separation of variables. Instead, the full $(L+1)K \times (L+1)K$ system must be solved.

A separable smoothing spline model may be constructed as follows. We decompose $UU^t$ into $O D O^t$ where $O$ is orthonormal and $D$ is diagonal. We then replace the growth curve model of Eqs. 2 & 3 with the equivalent model with $\alpha^{new} = \alpha^{old} O$ and $\vec{g}(\vec{u}, i)^{new} = O^t \vec{g}(\vec{u}, i)^{old}$. This is equivalent to replacing the old penalty function for the functions $f_\ell(t)$ with a matrix valued penalty function. The separable system splits the growth curve problem into $L + 1$ independent one dimensional problems.

For the separable problem, the one dimensional convergence of Cox (1984) results may be extended trivially.

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New York University.


