Nonparametric Methods for Longitudinal Data
Using Regression Splines

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June 17, 2009

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OUTLINE

• Part I: Regression Spline Smoothing
• Part II: Regression Spline Smoothing for Longitudinal Data
• Summary
Regression Spline Smoothing

OUTLINE for Part I

• Review of Parametric Regression Modelling
• Nonparametric Regression Model
• Nonparametric Smoothing Methods
• Regression Spline Modelling
Regression Spline Smoothing

Review of parametric modelling

Figure 1: Examples for parametric regression
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Polynomial Regression

- **Model** \( y_i = \Phi_0(x_i)^T \beta + \epsilon_i, i = 1, 2, \cdots, n \).

- **Polynomial basis vector** \( \Phi_0(x) = [1, x, x^2, \ldots, x^k]^T \)

- **Matrix form** \( y = X \beta + \epsilon \).

- **Easy to fit** \( \hat{\beta} = (X^T X)^{-1} X^T y \).
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Advantages for Parametric Regression Modelling

• Easy to fit

• Methods for estimation, hypothesis testing and prediction well established

Drawbacks for Parametric Regression Modelling

• Parametric models applied, e.g., linear or quadratic, must be valid

• Invalid parametric models may lead to misleading results
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The Motivating Data
The motorcycle data (Silverman 1985)

- Collected to study the crashed effects after the motorcycles hit by a stimulated impact
- **Dependent variable**: time after a stimulated impact with motorcycles
- **Response variable**: head acceleration of a PTMO (post mortem human test object), capturing the crash effects
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Figure 2: The motorcycle data
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Figure 3: Polynomial fits for the motorcycle data
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Nonparametric Regression Model
For a data set \((x_i, y_i), \ i = 1, 2, \cdots, n,\)

\[ y_i = f(x_i) + \epsilon_i, \quad i = 1, \cdots, n, \]

- \(f(\cdot)\) unknown but smooth, target for estimation
- \(f(x) = E(y_i | x_i = x)\), conditional expectation of the response
- \(E(\epsilon_i) = 0\) and \(\text{Var}(\epsilon_i) = \sigma^2\)
- It reduces to a parametric model if \(f(\cdot)\) is known except a parameter
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Nonparametric Smoothing Methods

- **Local Polynomial Kernel Smoothing** (Wand and Jones 1995, Fan & Gijbels 1996)
- **Regression Splines** (Eubank 1988)
- **Smoothing Splines** (Wahba 1990, Green and Silverman 1994)
- **P-splines** (Ruppert, Wand and Carroll, 2003)
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Figure 4: Regression spline fit for the motorcycle data
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Regression Splines

- The simplest smoothing technique available
- A natural generalization of the polynomial regression
- Easy to understand and implement
- Widely used in data analysis
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Motivation

• Polynomials are not flexible to model data in a big range

• They work well with a small range since within a small range, a Taylor’s expansion up to some order is valid

• One can divide a big range, say $[a, b]$ into a few of small intervals:
  $[\tau_r, \tau_{r+1})$, $r = 0, 1, \cdots, K$,

where **interior knots**: $\tau_r$, $r = 1, 2, \cdots, K$, **boundary knots**: $a, b$

$$a = \tau_0 < \tau_1 < \tau_2 < \cdots < \tau_K < \tau_{K+1} = b.$$
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Definition

- **A regression spline** is a piecewise polynomial
- It is a polynomial of some order within any two neighboring knots $\tau_r$ and $\tau_{r+1}$ for $r = 0, 1, \cdots, K$
- The spline is jointed together at knots properly
- The spline allows discontinuous derivatives at the knots.
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**Truncated power basis (TPB)**

- A regression spline can be constructed using a $k$-order TPB
- Given $K$ interior knots $\tau_1, \tau_2, \cdots, \tau_K$, the $k$-order TPB is
  $$1, x, \cdots, x^k, (x - \tau_1)^k_+, \cdots, (x - \tau_K)^k_+.$$
- The truncated power function $w^k_+ = [w_+]^k$, $w_+ = \max(0, w)$.
- First $k + 1$ basis functions are polynomials of order up to $k$
- Last $K$ basis functions are truncated power basis functions of order $k$
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**Regression splines** using TPB:

\[ f(x) = \sum_{s=0}^{k} \beta_s x^s + \sum_{r=1}^{K} \beta_{k+r} (x - \tau_r)^k. \]

- Within \([\tau_r, \tau_{r+1})\), \(f(x)\) is a \(k\)-order polynomial:

\[ f(x) = \sum_{s=0}^{k} \beta_s x^s + \sum_{l=1}^{r} \beta_{k+l} (x - \tau_l)^k, \]

- \(f^{(k)}(x)\) jumps at \(\tau_r\) with amount \(\beta_{k+r} k!\), i.e.,

\[ f^{(k)}(\tau_r^+) - f^{(k)}(\tau_r^-) = \beta_{k+r} k!. \]
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Figure 5: (a) a cubic truncated power basis ($k = 3$) with interior knots $.2, .4, .6,$ and $.8;$ and (b) three cubic regression splines.
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Regression Spline Model

- Denote as the TPB as
  \[ \Phi(x) = (1, x, \cdots, x^k, (x - \tau_1)^k_+, \cdots, (x - \tau_K)^k_+)^T \]
- A regression spline can be written as \( f(x) = \Phi(x)^T \beta \)
- The model \( y_i = f(x_i) + \epsilon_i, i = 1, \cdots, n \) becomes

\[ y = X\beta + \epsilon, \]

where \( X = (\Phi(x_1), \cdots, \Phi(x_n))^T. \)
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Regression Spline Smoother

- The LS estimator $\hat{\beta} = (X^T X)^{-1} X^T y$
- The RS smoother $\hat{f}(x) = \Phi(x)^T \hat{\beta}$
- The fitted response vector $\hat{y} = Ay$ with the RS smoother matrix $A = X(X^T X)^{-1} X^T$
- $A$ is a projection matrix satisfying $A^T = A$, $A^2 = A$ and $\text{tr}(A) = K + k + 1$. The trace of $A$ measures the RS model complexity
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Remarks for Nonparametric Regression

• For parametric regression, the model is fixed
• For nonparametric regression, the model is data-driven
• For the regression spline smoother, the model is specified by the TPB $\Phi(x)$
• The TPB $\Phi(x)$ is specified by the knot locations $\tau_1, \cdots, \tau_K$ and the number of knots, $K$
• Knot locating is important but the choice of the knot number is more important
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Two Widely Used Knot Locating Methods

**Equally Spaced Method** Take $K$ equally spaced points in the range of interest, say, $[a, b]$, as knots:

$$\tau_r = a + (b - a)r/(K + 1), r = 1, 2, \ldots, K.$$ 

- The method is independent of the design time points
- Employed when design time points are uniformly scattered
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Equally Spaced Sample Quantiles Method Use equally spaced sample quantiles of the design time points \( x_i, \ i = 1, 2, \cdots, n \) as knots:

\[
\tau_r = x_{(1+[rn/(K+1)])}, \ r = 1, 2, \cdots, K,
\]

- \( x_{(1)}, \cdots, x_{(n)} \) the order statistics of the design time points.
- \([a]\) denotes the integer part of \( a \).
- The method is design adaptive.
- More knots located where more design time points scattered.
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Knot Number Selection

Figure 6: RS fits to the motocycle data with different $K$. 
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A Criterion for Knot Number Selection
Generalized Cross-Validation (GCV)

- This method was modified from cross-validation (CV) method
- Use \( \text{SSE} = y^T(I_n - PX)y \) to measure goodness of fit
- Use \( \text{tr}(A) = K + k + 1 \) to measure model complexity
- \( \text{GCV} = \frac{\text{SSE}}{(1 - \text{tr}(A)/n)^2} \) trades off between goodness of fit and model complexity
- GCV often works well in choosing a good \( K \)
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Figure 7: $GCV$ for knot number selection for the motocycle data.
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Figure 8: Regression spline fit for the motorcycle data
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OUTLINE for Part II

- Review of LME Modelling
- Motivating Longitudinal Data
- Nonparametric Mixed-effects (NPME) Model
- Fitting the NPME Model Using Regression Splines
- Extensions to other Nonparametric/Semiparametric ME Models
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Review of the LME Model:

\[ y_{ij} = x_{ij}^T \beta + z_{ij}^T b_i + \epsilon_{ij}, \quad j = 1, 2, \cdots, n_i; \quad i = 1, 2, \cdots, n, \]
\[ b_i \sim N(0, D), \quad \epsilon_i \sim N(0, \sigma^2 I_{n_i}) \]

- \( x_{ij}, z_{ij} \): fixed-effects (FE) and random-effects (RE) covariates,
- \( \beta, b_i \): FE and RE vectors, modeling population and individual features respectively
- \( \epsilon_{ij} \): measurements errors
- \( D \) and \( \sigma^2 \): variance components
- Mixed-effects modelling allows to pull information across subjects to estimate \( \beta \) and \( b_i \)
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The LME Solution: Given the variance components $D$ and $R$,

$$
\hat{\beta} = (X^T V^{-1} X)^{-1} X^T V^{-1} y, \\
\hat{b} = DZ^T V^{-1} (y - X\hat{\beta}),
$$

with $X, Z$ properly defined,

- $\hat{\beta}$ is the generalized least squares estimator of $\beta$
- $V$ and $R$ are estimated using EM-algorithm (Vonesh and Chinchilli 1996)
- Existing software for solving LME models, e.g., *lme* in Splus and *Proc Mixed* in SAS.
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Advantages for LME Modelling

• Easy to fit
• Information across subjects and within subjects are used
• Methods for fitting the LME models well established

Drawbacks for LME Modelling

• Strong assumption about the model form needed
• Invalid parametric models may lead to misleading results
Motivating Longitudinal Data (Park and Wu 2004)

- Collected in an AIDS clinical study conducted by the AIDS Clinical Trials Group (ACTG), called ACTG 388 data.
- The study randomized 517 HIV-1 infected patients in three antiviral treatments. The data from one of the three treatments used
  - 166 patients treated with highly active antiviral therapy (HAART) for 120 weeks during which CD4 cell counts were monitored at weeks 4, 8, and every 8 weeks thereafter (up to 120 weeks)

- **Response variable**: CD4 cell counts as an important marker for assessing immunologic response of an antiviral regimen.

- **Covariate**: time after antiviral treatments
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The ACTG388 Data

![Raw Curves](image-url)
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Six Selected Subjects
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Nonparametric Mixed-effects (NPME) Model

\[ y_{ij} = \eta(t_{ij}) + v_i(t_{ij}) + \epsilon_{ij}, \quad j = 1, 2, \cdots, n_i; \quad i = 1, 2, \cdots, n, \]

\[ v_i(t) \sim \text{GP}(0, \gamma), \quad \epsilon_i = [\epsilon_{i1}, \cdots, \epsilon_{in_i}]^T \sim N(0, \sigma^2 I_{n_i}), \]

where

- \( \epsilon_{ij} \): \( j \)-th measurement error of \( i \)-th subject
- \( \eta(t) \): smooth FE function, modelling the popular feature
- \( v_i(t) \): smooth RE function, modelling the individual feature

**Aims:** Estimate \( \eta(t) \), \( \gamma(s, t) \) and \( \sigma^2 \)
Fitting the NPME model Using Regression Splines

- Approximating $\eta(t)$ by a regression spline $\Phi(t)^T \beta$
- Approximating $v_i(t)$ by regression splines $\Psi(t)^T b_i$
- $\Phi(t)$: order $k$ TPB with $K$ interior knots
- $\Psi(t)$: order $k_v$ TPB with $K_v$ interior knots
- $\beta$ and $b_i$ are the associated coefficient vectors
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The Approximation LME Model

\[ y_{ij} = x_{ij}^T \beta + z_{ij}^T b_i + \epsilon_{ij}, \quad j = 1, 2, \ldots, n_i; \quad i = 1, 2, \ldots, n, \]

\[ b_i \sim N(0, D), \quad \epsilon_i \sim N(0, \sigma^2 I_{n_i}) \]

- \( x_{ij} = \Phi(t_{ij}) \) and \( z_{ij} = \Psi(t_{ij}) \)

- For given \( \Phi(t) \) and \( \Psi(t) \), the approximation LME model can be fitted easily using existing software
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Remarks for NPME Modelling

- For parametric ME modelling, the model is fixed
- For NPME modelling, the model is data-driven
- For the regression spline-based approximation LME model, the model is specified by the TPBs $\Phi(t)$ and $\Psi(t)$
- The knots of $\Phi(t)$ and $\Psi(t)$ can be located using the two methods described in Part I
- Choosing the knot numbers, $K$ and $K_v$ to tradeoff the goodness of fit and model complexity
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Model Complexity and Goodness of Fit

- **FE and RE Predictions**: \( \hat{y} = X\hat{\beta} = Ay \) and \( \hat{v} = Z\hat{b} = A_v y \)

- **FE and RE Smoother Matrices**: \( A \) and \( A_v \)

- **FE and RE Model Complexity**: \( \text{df} = \text{tr}(A) \) and \( \text{df}_v = \text{tr}(A_v) \)

- **Goodness of fit**: Loglik (Log-likelihood)
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Criteria for Knot Number Selection: AIC and BIC

- **A Criterion** should trade off “Goodness of Fit” and “Model Complexity”

- For the regression spline-based NPME modelling, one may define
  
  - $\text{AIC}(K, K_v) = -2\text{Loglik} + 2(df + df_v + 1)$,
  
  - $\text{BIC}(K, K_v) = -2\text{Loglik} + \log(N)(df + df_v + 1)$.
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Applications to the ACTG 388 Data
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Plots of six individual fits
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Extensions to other Non/Semiparametric ME Models

- **Semiparametric ME Model:**
  \[
  y_{ij} = \eta(t_{ij}) + z_{ij}^T b_i + \epsilon_{ij}, \quad y_{ij} = x_{ij}^T \beta + v_i(t_{ij}) + \epsilon_{ij}.
  \]

- **Varying-coefficients ME Model:**
  \[
  y_{ij} = x_{ij}^T \beta(t_{ij}) + v_i(t_{ij}) + \epsilon_{ij}
  \]

- **Random-coefficient Model:**
  \[
  y_{ij} = x_{ij}^T \{\eta(t_{ij}) + v_i(t_{ij})\} + \epsilon_{ij},
  \]

- **Generalized Nonparametric ME Model:**
  \[
  y_{ij} = \phi\{\eta(t_{ij}) + v_i(t_{ij})\} + \epsilon_{ij}, \quad \text{where } \phi(\cdot) \text{ is known.}
  \]
Summary

- In Part I, we show how to fit a single curve using regression splines
- In Part II, we show how to fit a group of curves using regression splines
- Regression splines can be used to fit other non/semiparametric models
- Other smoothing methods can also be applied; see Wu and Zhang (2006) for details
That’s all!

THANK YOU VERY MUCH