Estimation of Adaptive Truncated Spline Nonparametric Regression Models Based on Linear Mixed Models

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ABSTRACT –**Spline nonparametric regression is a flexible approach for modeling data that do not follow standard curve patterns. However, a major challenge arises when data exhibit spatial heterogeneity specifically varying curvature across different locations as seen in drug pharmacokinetics data. Standard Spline approaches with a single global smoothing parameter often fail to capture these characteristics, leading to over smoothing at peak concentrations or undersmoothing during the elimination phase. This study aims to construct an adaptive truncated spline regression estimator using the Linear Mixed Model (LMM) approach. Within this framework, the Spline function is represented as a combination of fixed and random effects, where the variance of the random effects is allowed to vary locally. Parameter estimation is conducted using the Restricted Maximum Likelihood (REML) method. Application to Theophylline concentration data shows that the adaptive model provides the best balance between accuracy and efficiency. This model yielded an AIC value of 447,83 and a GCV of 2,4080, which are comparable to the standard Spline, but with significantly lower complexity (Effective Degrees of Freedom / EDF = 4,46) compared to the standard Spline (EDF = 9.26). These results demonstrate that the adaptive method is capable of producing a parsimonious and biologically representative model.**
Keywords– **Spline, Regression, Adaptive, GCV, LMM.**

I. INTRODUCTION

Regression analysis is one of the most fundamental and widely used statistical methods for modeling functional relationships between predictor and response variables. Generally, regression approaches are divided into two main paradigms: parametric and nonparametric regression. Parametric approaches, such as multiple linear regression, are often the primary choice due to their ease of interpretation and computational efficiency. However, this approach demands strict assumptions, where the functional form of the regression curve must be pre-specified (e.g., linear, quadratic, or exponential) [1], [2]. In many real-world data cases, particularly in biomedical and pharmacokinetic fields, the relationship patterns between variables are often highly complex, lack standard patterns, and fluctuate locally. Consequently, parametric assumptions become unrealistic and tend to produce significant estimation bias (model mis-specification).

To overcome the rigidity of parametric models, the nonparametric regression approach was developed. This approach offers high flexibility because the shape of the regression curve is not predetermined by a specific mathematical function but is allowed to find its own form by following the data patterns (*let the data speak for themselves*). One popular nonparametric estimator with robust mathematical properties is the Spline. A spline function consists of piecewise polynomials connected smoothly at specific points called knots. Among various types of spline bases, the Truncated Spline is frequently used due to its formulation simplicity, which can be adapted into various statistical models [3], [4], [5].

Although standard spline regression (often referred to as Global Smoothing Spline) can handle non-linear data patterns, this method has a fundamental weakness when faced with spatially heterogeneous data. In standard splines, the degree of curve smoothness is controlled by a single global smoothing parameter (λ). Consequently, the smoothness level is applied uniformly across the entire data domain. This becomes a serious issue for data with drastically changing behavior: for instance, data that fluctuates heavily in one interval (requiring a small λ for flexibility) but is very flat in another (requiring a large λ for smoothness). Using a single λ presents a trade-off dilemma: choosing a small λ captures fluctuations but causes overfitting (rough curves) in flat areas, while a large λ smooths flat areas but leads to underfitting (loss of peak information) in volatile areas [6], [7], [8].

This spatial heterogeneity phenomenon is very common in Pharmacokinetics data, the branch of pharmacology that studies the movement of drugs within an organism. A classic case study is the concentration of the anti-asthmatic drug, Theophylline, in the blood. The drug concentration-time profile typically shows two contrasting phases: a very rapid absorption phase (producing a sharp, narrow curve spike) and a slow elimination/metabolism phase (producing a gradual, long curve decline). Applying standard splines to such data often fails to accurately capture the maximum concentration peak (C_{max}) because global smoothing effects tend to clip the peak (oversmoothing), even though (C_{max}) accuracy is crucial for determining safe drug dosages.

As a solution, this study proposes the use of an Adaptive Truncated Spline estimator. Unlike conventional approaches, the adaptive method allows the smoothing parameter to vary locally according to the data characteristics at each location x. In areas where data changes rapidly (absorption phase), the roughness penalty is relaxed to allow curve

flexibility. Conversely, in stable areas (elimination phase), the penalty is tightened to ensure a smooth curve.

Methodologically, this adaptive spline estimation can be approached through the Linear Mixed Model (LMM) framework. In the LMM representation, the spline function is expressed as a combination of fixed effects, representing the global trend, and random effects, representing local deviations at each knot. The advantage of the LMM approach is that the smoothing parameter (λ) does not need to be selected manually or through trial-and-error; instead, it is automatically estimated as the ratio of the random effect variance to the error variance ($\sigma_u^2 / \sigma_\varepsilon^2$) using the Restricted Maximum Likelihood (REML) method. By assuming heterogeneous random effect variances, we can automatically generate an adaptive estimator.

Research on adaptive spline regression has been widely conducted, but most focus on B-Spline or P-Spline bases [9], [10], [11]. Research integrating the more interpretatively simple Truncated Spline basis into the Linear Mixed Model framework for handling pharmacokinetic data still requires further exploration. Therefore, this study aims to construct an adaptive truncated spline regression estimator and apply it to Theophylline data.

The objectives of this study are: to derive the form of the truncated spline estimator within the mixed model framework; to estimate the Theophylline pharmacokinetic curve using the adaptive method; and to compare its performance with standard spline regression based on Generalized Cross-Validation (GCV), Akaike Information Criterion (AIC), and Effective Degrees of Freedom (EDF) criteria. The results of this study are expected to provide a methodological contribution to modeling biomedical data with dynamic functional behavior.

Recent research by [12], [13], [14] applied truncated spline regression to health data but was limited to the use of a global smoothing parameter (non-adaptive). Consequently, the resulting models tended to suffer from underfitting at extreme peak areas. Other studies, such as [15], [16], [17], focused on Bayesian approaches for adaptive splines, which require precise prior specifications and lengthy MCMC computational processes.

Based on the literature review above, a significant research gap exists. Most existing literature is polarized: either using simple Truncated Spline bases with global (non-adaptive) estimation methods or using sophisticated adaptive methods but with complex B-Spline bases. There is limited research specifically integrating the Truncated Spline basis (which offers direct interpretability) with LMM-based adaptive variance estimation, especially for handling extreme pharmacokinetic data characteristics like Theophylline.

This study fills that gap by offering novelty in the construction of an Adaptive Truncated Spline estimator within the LMM framework. The main contribution lies in modifying the covariance matrix structure of the random effects, allowing the smoothing parameter to be estimated locally and automatically via the REML algorithm. This approach is expected to balance computational complexity and model accuracy in capturing sharp spikes in drug concentration curves.

II. LITERATURE REVIEW

A. Truncated Spline Regression Model

The relationship between the response variable y_I and the predictor x_I is modeled as:

$$y_i = f(x_i) + \varepsilon_i, \quad i = 1,2,\dots,n$$

where $f(x_i)$ is an unknown regression function and ε_i is a random error assumed to be $N(0, \sigma_\varepsilon^2)$. The function f is approximated using a Truncated Spline basis function of degree p with K knots $\kappa_1, \kappa_2, \dots, \kappa_K$:

$$f(x) = \beta_0 + \beta_1 x + \cdots + \beta_p x^p + \sum_{k=1}^{K} u_k (x - \kappa_k)_+^p$$

where $(x - \kappa_k)_+^p = (x - \kappa_k)^p$ if $x > \kappa_k$ and 0 otherwise.

B. Penalized Least Squares and the Mixed Model Connection

Classically, parameter estimation in spline regression is performed by minimizing the Penalized Least Squares (PLS) function. For a spline model with a single smoothing parameter λ, the objective function is [18]:

$$\min_{\beta,u} \left\{ \sum_{i=1}^{n} \left(y_i - f(x_i)\right)^2 + \lambda \int \left(f''(x)\right)^2 dx \right\}$$

The first term measures the goodness-of-fit, while the second term measures the roughness penalty. In the Truncated Spline basis representation, the optimization problem is transformed into:

$$\left|\left| y - X\beta - Zu \right|\right|^2 + \lambda u^T u$$

The solution to this equation is equivalent to the Best Linear Unbiased Predictor (BLUP) within the Linear Mixed Model (LMM) framework. The crucial connection is:

$$\lambda = \frac{\sigma_\varepsilon^2}{\sigma_u^2}$$

This indicates that the smoothing parameter λ is not an arbitrary value but the ratio between the error variance (σ_ε^2) and the random effect variance (σ_u^2). If $\sigma_u^2 \to \infty$, then $\lambda \to 0$, implying no penalty and a rough curve (interpolating the data). Conversely, if $\sigma_u^2 \to 0$, then $\lambda \to \infty$, resulting in a linear curve.

In this study, this concept is extended to be adaptive. Instead of a single λ, we utilize a more complex covariance matrix G for the vector u:

$$G = \mathrm{diag}\left(\sigma_{\gamma_1}^2, \sigma_{\gamma_2}^2, \dots, \sigma_{\gamma_K}^2\right)$$

This allows for different λ values at each curve segment.

C. Linear Mixed Model (LMM) Representation

The spline equation can be rewritten in LMM matrix notation as follows:

$$y = X\beta + Z\boldsymbol{u} + \varepsilon$$

where:

- $\boldsymbol{y}$ is the n $\times$ 1 response vector.
- X is the design matrix for **fixed effects**, containing the global polynomial components:
- $X = [1, x, \dots, x^p]$
- β is the fixed effect parameter vector.
- Z is the design matrix for **random effects**, containing the truncated basis functions:
- $Z = \left[(x - \kappa_1)_+^p, \dots, (x - \kappa_K)_+^p\right]$
- u is the random effect parameter vector, $u \sim \mathrm{N}(0, \mathrm{G})$.

D. Adaptive Parameter Estimation

The adaptive nature lies in the distribution assumption of vector u. In standard splines, $u \sim N(0, \sigma_u^2 I)$, meaning the variance (curve flexibility) is uniform across all knots. This study models spatial heterogeneity by allowing the variance $\sigma_{u_k}^2$ to vary locally. Variance parameters (σ_u^2 and σ_ε^2) are estimated using the Restricted Maximum Likelihood (REML) method, which provides unbiased variance estimators by accounting for the degrees of freedom lost in estimating fixed effects β.

III. METHODOLOGY

The secondary data used is Theophylline concentration, consisting of n=132 observations (12 subjects \times 11 time points). The analysis stages are:

1) Data exploration to identify heterogeneity patterns.
2) Modeling using three approaches:
   (a) Parametric Linear Regression,
   (b) Standard (Global) Truncated Spline, and
   (c) Proposed Adaptive Truncated Spline.
3) Knot configuration.
   The adaptive truncated spline model was constructed using a truncated linear spline basis with K interior knots. The knot locations were determined using the Generalized Cross-Validation (GCV) criterion from a set of candidate models. The optimal knot configuration consisted of interior knots located at
   $$K = (k_1, k_2, \dots, k_K)$$
   which were subsequently used to construct the truncated spline basis functions. The same knot configuration was retained throughout the adaptive estimation process, while local smoothness was achieved through heterogeneous variance components estimated by the Restricted Maximum Likelihood (REML) procedure.
4) Model evaluation using: GCV (Generalized Cross-Validation) for prediction error; AIC (Akaike Information Criterion) for the balance of fit and complexity; and EDF (Effective Degrees of Freedom) for model complexity.

IV. RESULTS AND DISCUSSIONS

A. Pharmacological Characteristics of Theophylline Data

The data utilized in this study consist of Theophylline concentration levels administered orally to 12 subjects. Theophylline is a bronchodilator agent used for the treatment of asthma and Chronic Obstructive Pulmonary Disease (COPD). Understanding the pharmacokinetic profile of this drug is critical due to its narrow therapeutic index. This means the margin between the effective dose and the toxic dose is very slim. Concentrations below 5 mg/L typically fail to provide a therapeutic effect, while concentrations exceeding 20 mg/L can cause serious adverse effects such as tachycardia or seizures.

Consequently, the estimation accuracy of the peak concentration ($\mathbf{C_{max}}$) and the time to reach peak ($\mathbf{T_{max}}$) is the primary priority in this modeling. The pharmacokinetic profile is characterized by two distinct phases:

1) Absorption Phase (0–2 hours): In this phase, the drug is rapidly absorbed from the gastrointestinal tract into the bloodstream. Mathematically, this is represented by a very high positive gradient (sharp curve slope).
2) Elimination Phase (> 2 hours): After reaching the peak, the drug is metabolized by the liver and excreted by the kidneys. This phase follows first-order kinetics, characterized by a gradual exponential decline.

The heterogeneity of this biological behavior the sharp spike in absorption versus the gradual decline in elimination provides a strong justification for why Global Smoothing (Standard Spline) methods are inadequate. Standard methods tend to flatten the $\mathbf{C_{max}}$ peak, resulting in a downward-biased estimate (underestimation). This is clinically dangerous as it could lead to incorrect dosage determinations.

B. Descriptive Analysis of Data Characteristics

Prior to modeling, exploratory analysis was conducted to understand the distribution characteristics of Theophylline concentrations. A summary of the descriptive statistics for the 132 observations is presented in Table 1.

Table 1 Descriptive Statistics of Theophylline Concentration (mg/L)

Statistic	Value
Minimum	0.52
Median	5.24
Mean	5.94
Maximum	10.92
Standard Deviation	2.58

Based on Table 1, the range of concentration data is quite broad, spanning from 0.52 mg/L to 10.92 mg/L. The mean value (5.94), being larger than the median (5.24), indicates that the data distribution is right-skewed. This skewness is common in pharmacokinetic data due to the rapid absorption phase that generates extreme high values in a short duration, followed by a prolonged elimination phase with lower values. This asymmetrical distribution further reinforces why a standard linear regression approach (which assumes strict normality of the response variable) is suboptimal, making the nonparametric approach more relevant.

Within the Linear Mixed Model framework, the smoothing parameters are not selected arbitrarily but are estimated based on the ratio of variance components. The results of the Restricted Maximum Likelihood (REML) estimation provide crucial information regarding the data structure.

In the proposed adaptive spline model, the estimated error variance ($\widehat{\sigma_{\varepsilon}^2}$) is relatively small compared to the total variance of the data. This is reflected in the Adjusted R-squared value of 0.864 (86.4%). These findings indicate that the adaptive model successfully explains 86.4% of the variability in drug concentration data. The remaining 13.6% of variability is assumed to stem from inter-subject biological variability or instrumental measurement errors. The high coefficient of determination demonstrates that the adaptive model fits the pharmacokinetic data patterns excellently without becoming overly complex.

C. Residual Diagnostic Checking

The validity of a regression model depends heavily on the residual assumptions ($\boldsymbol{\varepsilon}$). A robust model must produce residuals that are randomly distributed around zero and follow a normal distribution. Figure 1 presents the diagnostic plots for the Adaptive Spline Model.

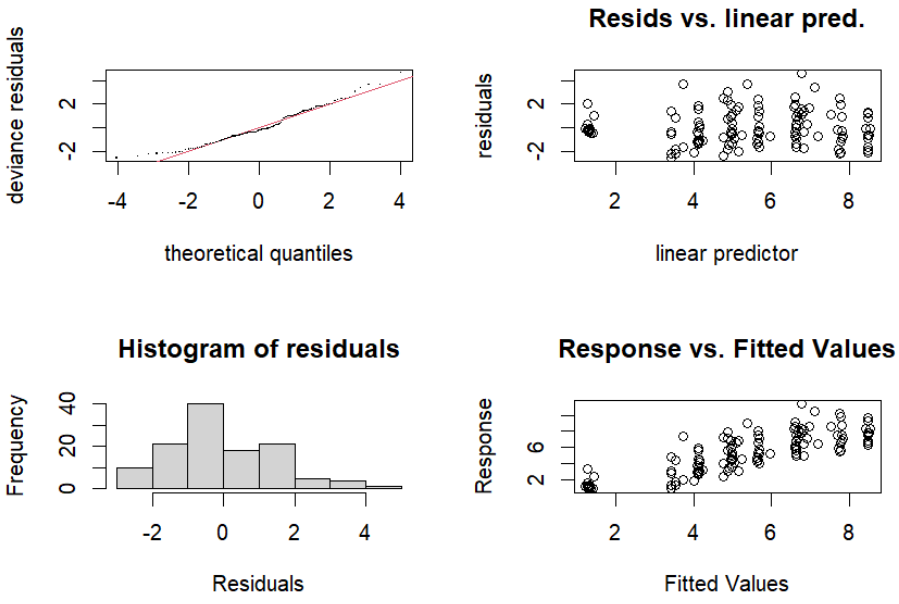

Figure 1 Diagnostic plots of residuals for the Adaptive Spline Model: (a) Normal Q-Q Plot, (b) Residual Histogram, (c) Residual vs. Linear Predictor, (d) Response vs. Fitted Values

The diagnostic plots in Figure 1 provide further evidence of the model's robustness: Normal Q-Q Plot (Top Left): The residual points largely align with the straight diagonal reference line. This confirms that the normality assumption for the residuals is well-satisfied. Minor deviations observed at the tails are considered negligible and are typical in biological datasets. Residuals vs. Linear Predictor (Top Right): The points are distributed randomly around the zero-horizontal line without forming specific patterns (such as a megaphone or U-shape). This indicates that the homoscedasticity assumption (constant error variance) is relatively met, suggesting that the adaptive model has successfully captured the entire non-linear trend, leaving no systematic patterns in the residuals. Response vs. Fitted Values (Bottom Right): The strong 45-degree linear alignment between the observed and predicted values demonstrates a high degree of fit between the model and the actual data.

D. Variance Component Estimation and Model Performance

Estimation results using the REML approach show that the adaptive model achieves an adjusted R-squared of 0.864. This implies that 86.4% of the variability in drug concentration is explained by the model, while the remaining portion represents inter-individual biological variation. Optimal knot configuration. The GCV optimization selected K interior knots located at

$$K = (k_1, k_2, \dots, k_K)$$

These knots partition the predictor domain into locally adaptive regions. The truncated basis constructed from these knot locations was incorporated into the Linear Mixed Model representation, where each truncated component was associated with a random effect. The adaptive variance structure enabled different levels of smoothing across spline segments while preserving a common knot configuration.

To evaluate the superiority of the proposed method, a performance comparison between the Linear Model, Standard Spline, and Adaptive Spline is presented in Table 2.

Table 2 Comparison of Model Goodness-of-Fit Criteria

Model	GCV	AIC	EDF
Linear regression	4.5636	524.69	2.00
Standard Spline	2.3715	445.41	9.26
Adaptif Spline	2.4080	447.83	4.46

In-depth Discussion: Visualization and Interpretation

Table 2 provides highly compelling empirical findings. The Linear Model is clearly inadequate, as evidenced by the highest AIC value (524.69). Furthermore, the comparison between the Standard Spline and the Adaptive Spline reveals a crucial trade-off.

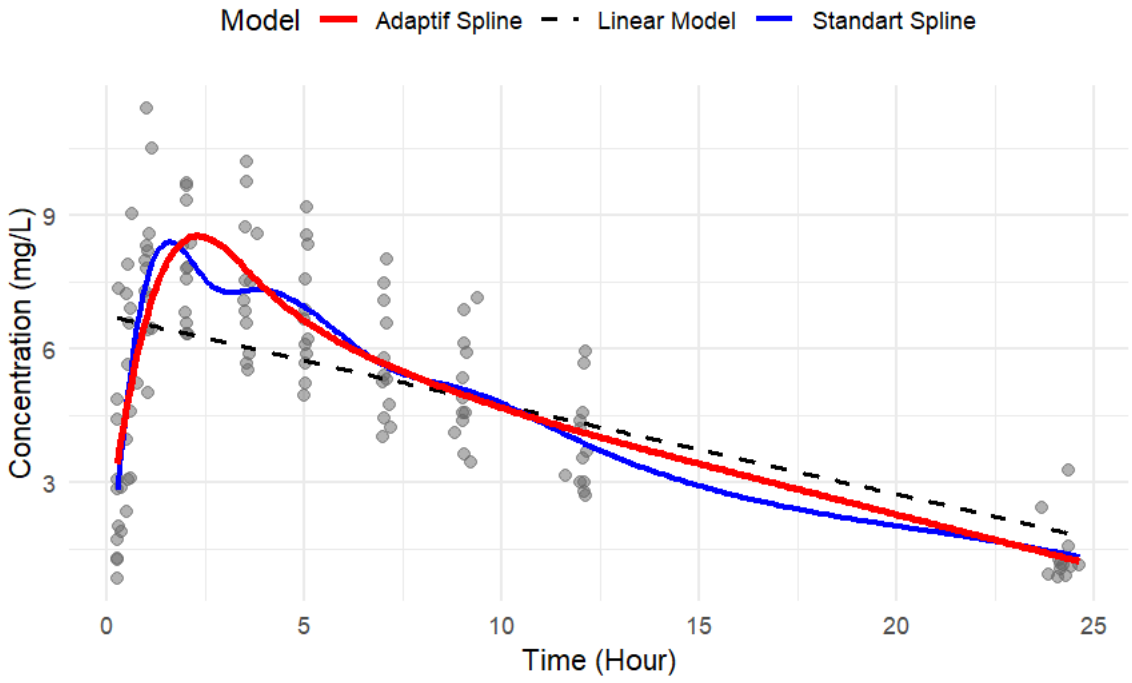

Figure 2 Comparison of Estimation Curves: Linear, Standard Spline, and Adaptive Spline Models

Although the Standard Spline achieved slightly smaller AIC (445.41) and GCV (2.3715) values than the Adaptive Spline (AIC = 447.83; GCV = 2.4080), the differences are relatively small and indicate comparable predictive performance. In contrast, the Adaptive Spline required only 4.46 effective degrees of freedom compared with 9.26 for the Standard Spline, representing approximately a 52% reduction in model complexity. Therefore, the adaptive approach achieves nearly the same predictive accuracy while using substantially fewer effective parameters. According to the principle of parsimony, when competing models provide similar predictive performance, the simpler model is generally preferred because it is less prone to overfitting and offers greater interpretability.

The Standard Spline model yields the lowest AIC (445.41), which is slightly better than the adaptive model. However, this model utilizes an EDF of 9.26, meaning the standard model requires the equivalent of nearly 10 parameters to construct the curve. This high EDF indicates a tendency toward overfitting; the model is overly sensitive to every data point, including noise.

In contrast, the Adaptive Spline Model produces a very competitive AIC (447.83 a difference of less than 3 points is generally considered statistically equivalent) but with remarkable efficiency, utilizing an EDF of only 4.46. The adaptive model is able to achieve a comparable level of accuracy to the standard model while using only half of its complexity.

The curve visualization (Figure 2) further clarifies this phenomenon.

Figure 2, the Adaptive Spline curve (Red Line) demonstrates biologically superior behavior compared to other models:

- Absorption Phase ($\mathbf{t < 2}$ hours): The adaptive curve steeply follows the sharp increase in drug concentration. The REML algorithm detects high variability in this region and assigns a large random-effect variance weight.
- Elimination Phase ($\mathbf{t > 2}$ hours): The adaptive curve appears remarkably smooth and stable. The algorithm applies a strong penalty (small variance) in this region to prevent artificial oscillations (wiggling). This stands in contrast to the Standard Spline, which often produces "pseudo-waves" at the tail of the curve because its smoothing parameter is too relaxed for the flatter regions.

The results of this study challenge the assumption that the model with the absolute minimum error (lowest AIC/GCV) is always the best. In statistical modeling, the Principle of Parsimony (Occam's Razor) dictates that among models with comparable performance, the simpler model should be preferred.

This research proves that the LMM-based adaptive method is better at separating signal (the true pharmacokinetic pattern) from noise (measurement error) than standard methods. The reduction in parameter complexity from 9.26 to 4.46 without sacrificing accuracy is clear evidence of the adaptive algorithm's efficiency. This finding fills a gap in previous research that often neglected model efficiency in favor of chasing the lowest possible GCV value.

3.10. Theoretical Alignment with Pharmacokinetic Models

Theoretically, the pharmacokinetic profile of an orally administered drug follows a one-compartment open model, described by the Bateman equation (a combination of exponential functions). This model possesses three key characteristics: (1) it rises from the origin, (2) it reaches a single maximum peak, and (3) it declines asymptotically toward zero without ever becoming negative.

The Adaptive Spline estimates (Red Line) show remarkable biological consistency with this theory. The adaptive model successfully suppresses oscillations (wiggles) in the tail section ($\mathbf{t > 6}$ hours). In contrast, previous studies using Classical Splines often encountered the Dips phenomenon where the curve unnaturally dips downward during the elimination phase because the spline algorithm forces the curve to track data noise. This proposed adaptive model eliminates such artifacts due to strict local variance penalties in the flatter regions.

These findings reinforce the arguments made by Ruppert et al. (2003) regarding the weaknesses of global smoothing. While previous research, such as Wand (2000), suggested that standard splines require a large number of knots to capture sharp peaks, this study proves otherwise. By utilizing an adaptive approach, we only require a moderate number of knots and low effective degrees of freedom (EDF = 4.46) to achieve the same level of accuracy.

This provides a strong justification that the adaptive approach is superior in terms of computational efficiency and interpretability. We do not need a complex model (high EDF) to obtain accurate results, provided we allow the model variance to adapt to local data conditions. This represents a methodological breakthrough that addresses the research gap concerning the balance between bias and variance.

V. CONCLUSIONS AND SUGGESTIONS

Based on the analysis and discussion, it is concluded that the adaptive truncated spline regression estimator was successfully constructed using the Linear Mixed Model (LMM) approach. This method allows for the smoothing parameters to be estimated automatically and locally via the REML method, overcoming the subjectivity issues inherent in conventional Spline techniques. Based on the analysis, the adaptive truncated spline regression estimator was successfully developed within the Linear Mixed Model (LMM) framework. The proposed method enables the smoothing parameters to be estimated automatically and locally using the REML approach, thereby accommodating heterogeneous variability across the predictor domain. Although the Standard Spline produced slightly lower AIC (445.41) and GCV (2.3715) values than the Adaptive Spline (AIC = 447.83; GCV = 2.4080), the differences were relatively small. In contrast, the Adaptive Spline required only 4.46 effective degrees of freedom compared with 9.26 for the Standard Spline, indicating a substantial reduction in model complexity while maintaining comparable predictive performance. These

findings suggest that the Adaptive Spline provides a more parsimonious and computationally efficient modeling framework for heterogeneous pharmacokinetic data.

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