On Designing Experiments for a Dynamic Response Modeled by Regression Splines

Rong Pan*

School of Computing, Informatics, and Decision Systems Engineering

Arizona State University, Tempe, Arizona, USA.

Moein Saleh

Paypal, Inc.

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Abstract

Dynamic response systems are often found in science, engineering and medical applications, but the discussion on experimental design for such a system is relatively rare in literature. For an experimenter, designing such experiments requires her to make decisions on (1) when or where to take response measurements along the dynamic variable and (2) how to choose the combination of experimental factors and their levels. The first consideration is unique for such experiments, especially when the measurement cost is high. In this paper, we present a design approach through the mixed effects linear model, which is based on a hierarchical B-spline function for the dynamic response. We develop several theorems that can assist in finding a statistically efficient sampling plan and propose an algorithm for searching the D-optimal design of a dynamic response system.

Keywords: Optimal experimental design, dynamic system, B-splines, exchange algorithm.

*corresponding author: rong.pan@asu.edu

1. Introduction to the B-spline Function

Many industrial experiments produce one or more dynamic responses, where the response is a function of time or another continuous variable, i.e., a response curve. In some cases a summary statistic of this function, such as the average response or the maximum response, will be sufficient for analyzing the system under study. There are many other occasions, however, when the experimenter desires to know the entire response curve so as to understand the dynamics of the system under study. Thus, it requires to model the system response by some flexible, yet mathematically tractable, response functions. The optimal experimental designs that target this type of dynamic response, as opposed to a scalar response variable, had rarely been discussed in literature before. In this paper, we present a mixed effects linear modeling approach to this problem and attempt to derive optimal designs under this modeling framework.

A class of commonly used mathematical functions for describing system dynamics are polynomial regression functions. Even though a polynomial function is good at modeling a response variable's global features, such as trend, curvature, etc., it is not flexible enough to capture local features. In addition, a higher-order polynomial often overfits the data. Figure 1 plots such a data set where the response variable demonstrates different dynamic behaviors in different regions. This type of data is referred as the whiplike structured data in Ruppert [33]. One may notice that there are several peaks and valleys at different time instances and with different magnitudes. Neither a second-order polynomial nor a third-order polynomial can capture these local features very well. Instead, a B-spline function looks generally better than those polynomial functions. Therefore, we will first describe B-spline regression functions in this section and demonstrate some properties of this class of regression functions.

A regression spline can be viewed as a piecewise polynomial regression, in which the entire response region is divided into multiple segments by interior knots and the data within each segment is fitted by a local polynomial function. Each local polynomial function is able to model response dynamics within its corresponding region, while the overall connectivity and smoothness of response curve are obtained by imposing some constraints at the end points (knots) shared by two adjacent local polynomials. These boundary constraints typically require the response curve to be continuous at these knots, which leads to the values of two adjacent

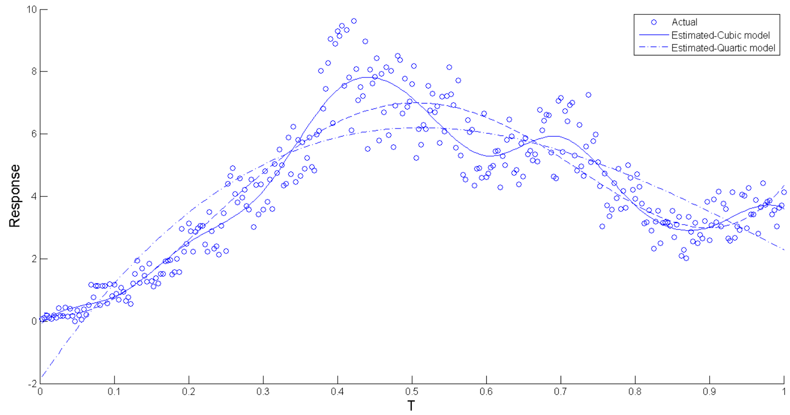

Figure 1: Whiplike structured data. The complexity of the dataset changes significantly at $T = 0.4$.

polynomial functions should coincide at interior knots. Furthermore, to guarantee a smooth curve up to visual inspection, it also requires the first and second derivatives of two adjacent functions must meet at knots. Cubic polynomial functions are able to satisfy these constraints, thus they are commonly used for constructing regression splines; i.e., cubic splines.

It is easy to construct a spline function by using truncated power basis functions. To estimate regression coefficients, however, this approach is computationally unstable. Instead, a class of basis functions that are recursively constructed, as discovered by de Boor [5], are widely adopted for modeling splines. A B(asis)-spline function is expressed as a linear combination of a set of basis functions.

Without loss of generality, let a function $f(t)$ span over a dynamic variable (e.g., time) t from 0 to 1. Suppose there are n interior knots and the piecewise polynomial functions should maintain continuity and smoothness at these knots and each piecewise polynomial function has a degree of d ($d = 3$ for cubic splines). The B-spline function is of order m, where $m = d + 1$. Expanding the knot set by adding m additional knots at each end of the dynamic variable and ordering these knots, we have an ordered knot series such as $\{\tau_0, \tau_1, ..., \tau_{n+2m-1}\}$, where $\tau_0 = \tau_1 = ... = \tau_{m-1} = 0$, $\tau_{n+m} = \tau_{n+m+1} = ... = \tau_{n+2m-1} = 1$, and other knots are interior knots. Then, the m-order B-spline bases are given by (de Boor [5]):

$$B_{i,1}(t) = \begin{cases} 1 & \tau_i \leq t < \tau_{i+1} \\ 0 & \text{otherwise} \end{cases}$$

$$B_{i,j}(t) = \frac{t-\tau_i}{\tau_{i+j-1}-\tau_i} B_{i,j-1}(t) + \frac{\tau_{i+j}-t}{\tau_{i+j}-\tau_{k+1}} B_{i+1,j-1}(t), \tag{1}$$

where i ($i = 0, 1, ..., n+d$) is the index of basis function and j ($j = 1, 2, ..., m$) is the index of spline order. By Eq.(1), one can see that the basis function of higher order can be recursively constructed by the basis functions of lower order.

A B-spline function of order m, $f_m(t)$, is defined as

$$f_m(t) = \sum_{i=0}^{n+d} \theta_i B_{i,m}(t), \tag{2}$$

where θ_i is the coefficient of the corresponding basis function of order m, $B_{i,m}$. To simplify the notation, we will drop the subscript m in Eq. (2) in the rest of this paper.

From Eq. (2) one can see that an order-m B-spline function with n interior knots is constructed by p (where $p = n+m$ or $p = n+d+1$) non-zero basis functions. It can be shown that the sum of these basis functions at any time t equals to 1. In addition, these basis functions are compact in the sense that each of them has non-zero values only within at-most m consecutive segments. For example, consider an order-4 B-spline function that has polynomial bases with degrees of 3 (i.e., a cubic spline), when there are three interior knots, the number of basis functions is 7 and each basis function has non-zero values within at-most 4 segments. Figure 2 (a) shows a set of order-4 B-spline basis functions with interior knots at $\{0.3, 0.6, 0.9\}$. Notice that the differentiability at these knots can be reduced by adding replicates. For example, Figure 2 (b-d) have additional 1, 2 and 3 replicates of knot 0.6, respectively, which result in a basis system that has one-degree continuous derivative, zero-degree continuous derivative but continuous function, and discontinuous function, respectively, at this point.

Using B-splines to model a dynamic response yields

$$Y(t) = f(t) + \varepsilon = \boldsymbol{B}^T(t)\boldsymbol{\theta} + \varepsilon, \tag{3}$$

where $\boldsymbol{B}^T(t)$ is the transpose of a basis function vector evaluated at t, $\boldsymbol{\theta}$ is a vector of coefficients, and ε is the measurement error with $\varepsilon \sim N(0, \sigma^2)$. Suppose there are N dynamic response profiles and each profile is measured at $t_1, t_2, ..., t_M$, then the response vector of each profile is $\mathbf{y}_j = [y_j(t_1), y_j(t_2), ..., y_j(t_M)]^T$, where $j = 1, 2, ..., N$. Let the response matrix be as $\mathbf{Y} = [\mathbf{y}_1, \mathbf{y}_2, ..., \mathbf{y}_N]$, then

$$\mathbf{Y}(\mathbf{t}) = \mathbf{B}(\mathbf{t})\boldsymbol{\Theta} + \boldsymbol{\varepsilon}, \tag{4}$$

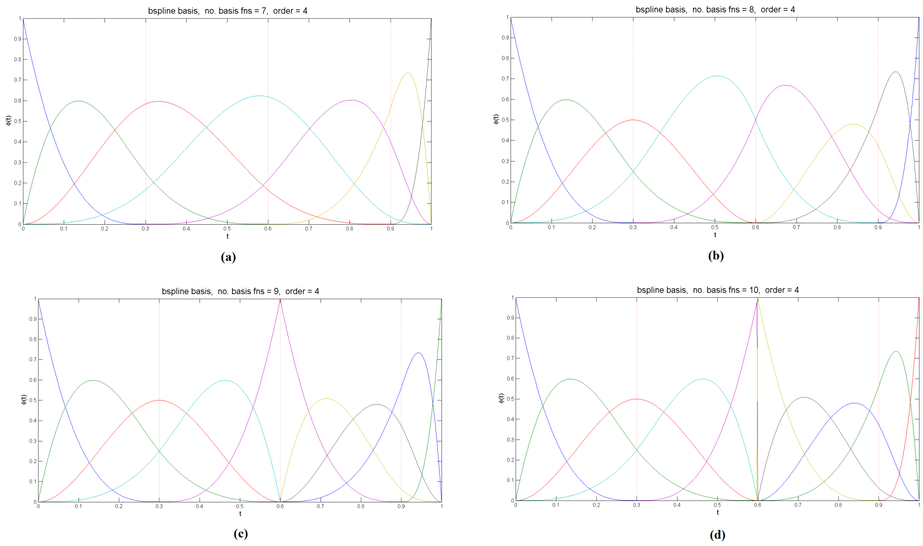

Figure 2: The order-4 B-spline system with 7,8,9 and 10 basis functions that are derived from the internal knots located at $\{0.3, 0.6, 0.9\}$,$\{0.3, 0.6, 0.6, 0.9\}$, $\{0.3, 0.6, 0.6, 0.6, 0.9\}$ and $\{0.3, 0.6, 0.6, 0.6, 0.6, 0.9\}$, respectively.

where $\mathbf{B}(\mathbf{t})$ is the design matrix of basis functions and its elements are as $b_{ik} = B_k(t_i)$, where $i = 1, 2, ..., M$ and $k = 1, 2, ..., p$, $\boldsymbol{\Theta}$ is the corresponding matrix of coefficients, and $\boldsymbol{\varepsilon} \sim N(\mathbf{0}, \boldsymbol{\Sigma})$. Note that $\mathbf{Y}(\mathbf{t})$ is a $M \times N$ matrix, while $\mathbf{B}(\mathbf{t})$ and $\boldsymbol{\Theta}$ have $M \times p$ and $p \times N$ dimensions, respectively. As aforementioned, the sum of all elements in each row of $\mathbf{B}$ matrix equals to one. This constraint needs to be accommodated during the development of any efficient algorithm for finding optimal designs.

The remainder of the paper is organized as follows. The design problem to be studied in this paper will be specified in the next section and a mixed effects linear model framework will be presented. In Section 3, some basic theorems derived from the B-spline model are stated and they provide the foundation for finding optimal sampling times. Next, a novel search algorithm is developed in Section 4, which focuses on the planning of sampling times on a response curve. Section 5 describes another algorithm for sequentially generating optimal sampling times and optimal experimental conditions. Finally, the performance of optimal designs obtained by our algorithms will be compared with other designs through an example.

2. Experimental Design Issues

2.1 Literature Review

In this paper we discuss the experimental design for a dynamic response. The design issues involve determining 1) the sampling time of dynamic response variable and 2) the experimental condition to be set on input or controllable variables.

Optimal designs, in which some specific experimental designs are found by optimizing certain statistical criteria (see, e.g., [20, 21, 22]), for such dynamic response experiments will be studied in this paper. Among many optimality criteria, D-optimality is the most popular one for evaluating the quality of a design, particularly when the experimenter is interested in the quality of model parameter estimation, because the D-optimal criterion maximizes the determinant of expected Fisher information matrix of parameter estimators. Fedorov et al.[7] introduced the point exchange algorithm (PEA) for constructing exact D-optimal designs for linear models. This algorithm and its variants are widely adopted by existing statistical software (see, e.g., [1], [4], [28], [29], [31], [32], [37], [41] and[45]). The PEAs proposed by these researchers take the exhaustive search approach to finding the optimal design from a large set of candidate designs. Generating and storing the candidate matrix and comparing each candidate design point with others may impose a huge computational burden in many optimal design problems. Therefore, some meta-heuristic optimization algorithms, such as genetic algorithm (GA) and simulated annealing (SA) algorithm, have been proposed for obtaining optimal experimental designs (see, e.g., [3], [15], [17] and [26]). On the other hand, the coordinate exchange algorithm (CEA) proposed by [27] has been used to address the PEA's shortcoming by avoiding an explicit list of candidate design points. Until today, this type of algorithm is still one of the most popular algorithms for constructing D-optimal designs for linear and nonlinear models.

While the optimal experimental designs for static responses have been widely discussed in the literature, the research on experimental designs for dynamic responses is relatively sparse. To design the experiment with a dynamic response, one needs to select a set of response measurement points (sampling points) on the dynamic variable, as well as the setting of other experimental factors. These two aspects may be considered separately or jointly. Most of the existing literature on experimental designs for dynamic responses focused on the first aspect only, i.e., the response measurement locations or the sampling times on the response curve. Gaffke and Heiligers [10] used B-spline bases for modeling response curves and then found the D-optimal design for dynamic response. Woods et al. [43] considered an additional interaction term of B-spline bases and ordinary polynomial models. Heiligers [16] utilized Chebyshev splines for designing E-optimal experiments with dynamic responses. Finding the D_s and T optimal sampling times for functional data was also discussed by Fisher and Woods [9]. Our proposed algorithm extends these approaches by considering both experimental settings and sampling times via an mixed effects modeling method of dynamic response. This method is developed from the hierarchical modeling approach to fitting dynamic data, as suggested by [6], [30], [36] and [44]. We also note that mixed effects models have been widely studied in the longitudinal data analysis (see, e.g., [23] and [39]).

For the completeness of the description of dynamic system modeling, we need to mention that the response model presented in this paper is different from the time-invariant dynamic system as represented by the time series model or Box-Jenkins transfer function model [2]. Here, we utilize an explicit mathematical expression of response variable (i.e., a spline function) as a function of time and some static input variables; while in the transfer function model, the dynamics of the response is modeled by a function of past responses and dynamic input variables. The study of experimental design for transfer function model can be traced back to Viort [40]. Titterington [35] surveyed the applications of optimal experimental design theory to such models and built a connection of optimal process control and design of experiments. This body of work is also related to system identification, which deals with the problem of building mathematical models of dynamical systems based on observed system data, appeared in the system control literature (see, e.g., Ljung [25]). More recently, Georgakis [11] investigated the experimental design problem for a system where the response was static but decision variables were time-varying processes and modeled by a linear combination of Legendre polynomial basis functions, so the design problem became as determining the input variable profiles. They named this type of design problem as Design of Dynamic Experiments (DoDE) and demonstrated its uses in chemical and pharmaceutical industries (see [8] and [12]). Again, our study is different from theirs, because our study focuses on the dynamics of response variable, thus the response sampling time.

2.2 Mixed effects model

Beside of specifying the sampling points on the dynamic variable, the experimental design of a dynamic response system concerns with the study of effects of experimental factors on the system's dynamic behavior. To model these effects, a popular approach is the hierarchical modeling approach, in which the coefficients of spline model (Eq. (4)) are defined as functions of experimental factors (see, e.g., [6], [36], [39] and [44]).

Consider an experiment that consists of multiple treatments on experimental units and the outputs from each experimental unit are measured over time. The hierarchical modeling approach has two stages – first, the response curve of each experimental unit is modeled by a spline function; second, the coefficients of spline function are modeled as functions of treatments.

This approach yields:

$$\mathbf{y}_j = \mathbf{B}(\mathbf{t})\boldsymbol{\theta}(\mathbf{x}_j) + \boldsymbol{\epsilon}_j \quad \boldsymbol{\epsilon}_j \sim N(0, \boldsymbol{\Sigma}), \tag{5}$$

and

$$\boldsymbol{\theta}(\mathbf{x}_j) = \mathbf{H}\mathbf{f}(\mathbf{x}_j) + \boldsymbol{\omega}_j \quad \boldsymbol{\omega}_j \sim N(0, \boldsymbol{\Sigma}_\omega), \tag{6}$$

where $\mathbf{x}_j$ is the vector of experimental factors applied on the j^{th} experimental unit and $\mathbf{f}(\mathbf{x}_j)$ is the vector of any possible transformation of these experimental factors in linear regression, and $\mathbf{H}$ is a matrix of unknown model parameters. Same as before, we assume there are M measurements on the j^{th} response curve, so $\mathbf{y}_j$ is a $M \times 1$ vector, $\mathbf{B}(\mathbf{t})$ is a $M \times p$ matrix, where p is the number of basis functions, and $\boldsymbol{\theta}(\mathbf{x}_j)$ is a $p \times 1$ vector. Assuming there are q linear regression terms in Eq. (6), then $\mathbf{f}(\mathbf{x}_j)$ is a $q \times 1$ vector and $\mathbf{H}$ is a $p \times q$ matrix. By this hierarchical modeling approach, the stage-1 model smooths the actual observed data profile, $\mathbf{y}_j$, individually; then, the stage-2 model assesses the relationships between smoothing parameters and experimental factors.

Del Castillo et al. [6] and Verbeke and Molenberghs [39] proposed to combine Equations (5) and (6) to derive the mixed effects model such as

$$\begin{aligned}\mathbf{y}_j &= \mathbf{B}(\mathbf{t})[\mathbf{H}\mathbf{f}(\mathbf{x}_j) + \boldsymbol{\omega}_j] + \boldsymbol{\epsilon}_j \\ &= \mathbf{B}(\mathbf{t})\mathbf{H}\mathbf{f}(\mathbf{x}_j) + \mathbf{B}(\mathbf{t})\boldsymbol{\omega}_j + \boldsymbol{\epsilon}_j, \end{aligned} \tag{7}$$

Using a Kronecker product of two matrices, the first term of the right hand side of Eq.(7) can be rewritten as $(\mathbf{f}(\mathbf{x}_j)^T \otimes \mathbf{B})\mathbf{vec}(\mathbf{H})$, where the $\mathbf{vec}()$ operator stacks columns of $\mathbf{H}$ to one column. Then, the mixed effects model of the j^{th} dynamic response becomes

$$\mathbf{y_j} = \mathbf{X}_j\boldsymbol{\beta} + \mathbf{B}\boldsymbol{\omega}_j + \boldsymbol{\epsilon}_j, \tag{8}$$

where $\mathbf{X}_j = \mathbf{f}(\mathbf{x}_j)^T \otimes \mathbf{B}$ and $\boldsymbol{\beta} = \mathbf{vec}(\mathbf{H})$. Note that $\mathbf{X}_j$ has the dimensions of $M \times pq$ and $\boldsymbol{\beta}$ has the dimensions of $pq \times 1$. It is easy to show the variance of $\mathbf{y}_j$ is given by $\mathbf{V}_j = \boldsymbol{\Sigma} + \mathbf{B}(\mathbf{t})\boldsymbol{\Sigma}_w\mathbf{B}(\mathbf{t})^T$.

When there are multiple experimental units and each of them generates one response curve, we can stack the measurements of these curves to form a response vector, then the mixed effects model becomes

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + (\mathbf{I}_N \otimes \mathbf{B})\boldsymbol{\omega} + \boldsymbol{\epsilon}. \tag{9}$$

Here, $\mathbf{Y}$ is a vector of all response measurements such as $\mathbf{Y} = [\mathbf{y}_1^T, \mathbf{y}_2^T, ..., \mathbf{y}_N^T]^T$. Same as before, we assume there are N experimental units and each of them is measured M times, then $\mathbf{Y}$ has the dimensions of $NM \times 1$. Again, let p be the number of basis functions and q the number of (transformed) experimental factor terms, it can be shown that the design matrix $\mathbf{X}$, which is constructed by $(\mathbf{I}_N \otimes \mathbf{B})\mathbf{F}(\mathbf{x})$ with $\mathbf{I}_N$ being an $N \times N$ identity matrix and $\mathbf{F}(\mathbf{x}) = [\mathbf{I_p} \otimes f(\mathbf{x_1}), \mathbf{I_p} \otimes f(\mathbf{x_2}), ..., \mathbf{I_p} \otimes f(\mathbf{x_N})]^T$, has the dimensions of $NM \times pq$. The fixed unknown parameters of this model, $\boldsymbol{\beta}$, is equal to $[\boldsymbol{\beta}_1^T, \boldsymbol{\beta}_2^T, ..., \boldsymbol{\beta}_p^T]^T$, where $\boldsymbol{\beta}_k^T = [\beta_{k1}, \beta_{k2}, ..., \beta_{kq}]$. Hence, $\boldsymbol{\beta}$ has the dimensions of $pq \times 1$. Finally, the unknown random effects term, $\boldsymbol{\omega}$, is equal to $[\boldsymbol{\omega}_1^T, \boldsymbol{\omega}_2^T, ..., \boldsymbol{\omega}_N^T]^T$, where $\boldsymbol{\omega}_j^T = [w_{j1}, w_{j2}, ..., w_{jp}]$ and $\boldsymbol{\omega}$ is a $Np \times 1$ vector.

The maximum likelihood estimate of unknown parameters in the mixed effects model provided above is

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}^T\mathbf{V}^{-\mathbf{1}}\mathbf{X}^T)^{-1}\mathbf{X}^T\mathbf{V}^{-\mathbf{1}}\mathbf{y}. \tag{10}$$

where $\mathbf{V} = \Sigma + (\mathbf{I_N} \otimes \mathbf{B})\Sigma_{\boldsymbol{\omega}}(\mathbf{I_N} \otimes \mathbf{B})^T$.

These estimators are unbiased to the parameters being estimated. The covariance of these estimators is given by

$$COV(\hat{\boldsymbol{\beta}}) = (\mathbf{X}^T\mathbf{V}^{-\mathbf{1}}\mathbf{X})^{-1}. \tag{11}$$

To obtain a D-optimal experimental design, one needs to minimize the determinant of $COV(\hat{\boldsymbol{\beta}})$ or to maximize the determinant of information matrix; therefore, the D-optimal criterion is defined as

$$D_{\boldsymbol{\beta}} := \max_{\mathbf{X}} |\mathbf{X}^T\mathbf{V}^{-\mathbf{1}}\mathbf{X}|. \tag{12}$$

Mixed effects models have been applied on a wide variety of experimental design studies. For examples, Goos and Jones [13] used this model for designing split-plot experiments; Laird and Ware [23] used it to study the repeated measurement problem; Liu and Frank [24], Kao et al. [19] and Saleh et al. [34] applied it on fMRI experiments. However, the experimental response to be considered in this paper is much more complicated than those in previous studies. We will derive the optimal experimental plan for both the sampling time of dynamic response and the setting of experimental factors on individual experimental unit.

The design matrix of mixed effects model, $\mathbf{X}$, is a sparse matrix. This matrix is constructed by the multiplication of stacked basis matrix $\mathbf{B}$ and experimental design points $\mathbf{f}(\mathbf{x})$. According to B-spline's basis properties, the basis function of order-m B-spline are nonzero only at the at-most m adjacent intervals separated by knots. Therefore, in the case of using an order-4 B-spline function (cubic spline) to model a dynamic response with 10 interior knots, there are 14 basis functions, but each basis function has non-zero values in at-most 4 adjacent intervals only, so at any sampling point there are at-most 4 non-zero basis values. Note that, if there is one sampling point in each interval, the basis matrix will become a banded diagonal matrix with a bandwidth of 4. For example, in the experiment given by Grove, Woods, and Lewis [14] there are 55 experimental units, 3 independent factors, and 7 observations on each response curve. Using the order-4 B-spline model yields a design matrix of size 385×21 $((NM) \times (pq))$. To make all model parameters estimable, only 385 nonzero entries are needed in this matrix, which is 5% of the size of design matrix.

3. Basic Theorems

In this section, we discuss the D-optimal sampling times for functional data in order to estimate the $\boldsymbol{\theta}$ parameter vector in Eq. (4) accurately. The covariance matrix for this linear model equals

$$COV(\hat{\boldsymbol{\theta}}) = (\mathbf{B}^T\mathbf{B})^{-1}$$

where $\mathbf{B}$ is the basis matrix that depends on the choice of sampling times, as well as the B-spline system to be used and the specification of interior knots.

Therefore, the D-optimal criterion can be specified as

$$D_\theta := \max_{\mathbf{B}} |\mathbf{B}^T\mathbf{B}| \tag{13}$$

$$S.T. \quad \mathbf{b}_i\mathbf{1} = 1, \quad \textit{for all } i\textit{'s}.$$

where $\mathbf{b}_i$ is the i^{th} row of $\mathbf{B}$ matrix and it is defined by $\mathbf{b}_i = [B_1(t_i)\ B_2(t_i)...\ B_p(t_i)]$, where $i = 1, 2, ..., M$. Note $B_k(t_i)$ is given by Eq. (1) evaluated at the sampling time t_i. Here, again, it is assumed that there are a total of M sampling times. The constraint in Eq. (13) simply states that each row of B must sum to unity.

To provide a general idea of what an optimal sampling plan would be like for a B-spline model, we plot two different B-spline basis systems in Figure 3 and Figure 4, along with their optimal sampling times. One can see these optimal sampling times are either on or close to the locations where one basis function has its maximum value. This property can be explained by the following theorems. The proof of the first theorem is provided in Appendix.

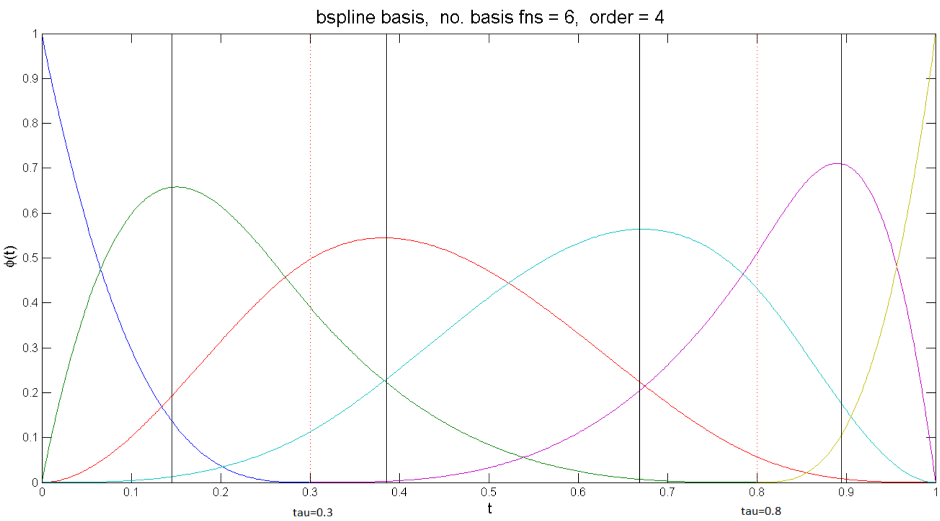

Figure 3: Plot of six bases for an order-4 B-spline system with internal knots (τ's) located at $\{0.3, 0.8\}$. Optimal sampling times are depicted by solid lines, while the dotted lines indicates the location of interior knots. Optimal sampling times are found to be $\{0, 0.145, 0.385, 0.669, 0.895, 1\}$.

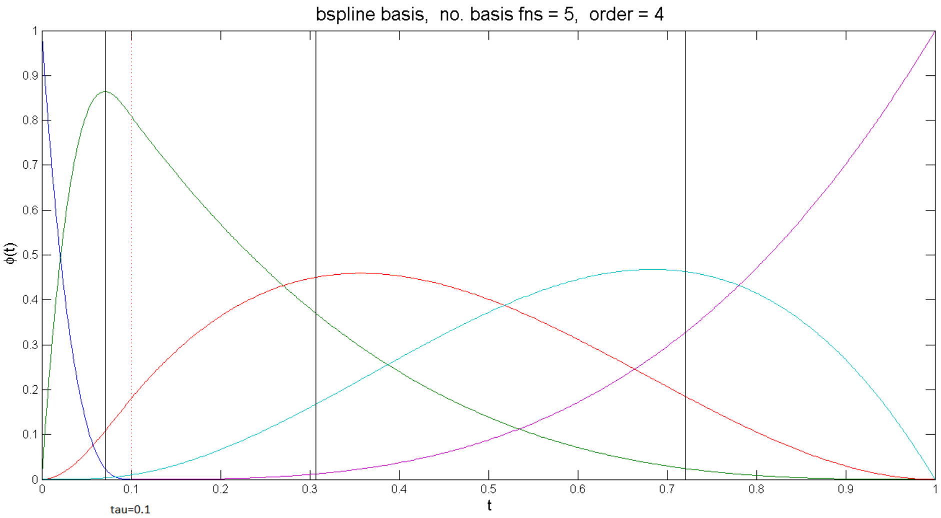

Figure 4: Plot of five bases for an order-4 B-spline system with internal knot (τ) located at $\{0.1\}$. Optimal sampling times are depicted by solid lines, while the dotted lines indicates the location of interior knots. Optimal sampling times are found to be $\{0, 0.071, 0.307, 0.72, 1\}$.

Theorem 3.1 *Let* $\mathbf{M}$ *be a symmetric matrix with non-negative elements. If* $\mathbf{M}$ *is positive definite, then there exists a positive value,* ω_T*, such that the determinant of* $\mathbf{M}$ *can be calculated by*

$$|\mathbf{M}| = \prod_i m_{ii} - \omega_T, \tag{14}$$

where m_{ii}*'s are the diagonal elements of* $\mathbf{M}$.

The proof can be extended from the Cauchy's expansion of the determinant of a positive definite matrix. As one can see from Appendix, the positive value ω_T involves non-diagonal elements in $\mathbf{M}$. As a result, to maximize the determinant function, we may try to increase the values of diagonal elements and reduce the values of non-diagonal elements at the same time. Now, consider the B-spline basis matrix defined in Eq. (13) and let $\mathbf{M} = \mathbf{B}^T\mathbf{B}$, so $\mathbf{M}$ is the information matrix of B-spline design matrix. It is easy to show that the summation of all elements in $\mathbf{M}$ is given by $\sum_i \sum_j m_{ij} = M$, where M is the number of rows of $\mathbf{B}$ or the number of sampling times. This property implies that increasing the values of diagonal elements in $\mathbf{M}$ will simultaneously decrease the values of non-diagonal elements in $\mathbf{M}$.

Theorem 3.2 *Let* $\mathbf{t} = \{t_1, t_2, ..., t_M\}$ *be an ordered sequence of optimal sampling times for a dynamic system modeled by a B-spline function, then the two end points of the dynamic variable must be included in this sequence, i.e.,* $t_1 = 0$ *and* $t_M = 1$.

This theorem is a direct consequence of the previous theorem when it is applied on the B-spline basis matrix. Suppose $\mathbf{B}$ is the design matrix without including $t = 0$ or $t = 1$ sampling time. Based on the Cauchy's expansion theorem and also Laplace's formula, a D-optimal design can be found by increasing the diagonal elements in $\mathbf{B}^T\mathbf{B}$ and decreasing non-diagonal elements at the same time. The constant summation property of a row of B-spline basis matrix indicates that replacing a row in the design matrix by another one does not change the summation of the elements in the information matrix. Since it is desired to increase the values of diagonal elements, changing the first row of $\mathbf{B}$ to be [1 0 0 ... 0] and the last row to be [0 0 ... 0 1] will increase the determinant of information matrix. Thus, $t = 0$ and $t = 1$ must exist in the sequence of optimal sampling times.

We can apply the same argument to other sampling times in the optimal sequence. As the spline function is supported by N bases, it requires at least N sampling times to make all coefficients estimatable. To have the diagonal elements of information matrix to be large while non-diagonal elements to be small, the corresponding diagonal elements in $\mathbf{B}$ should be large, which implies that optimal sampling times should be located around the time when one basis function reaches its maximum. This speculation has been supported by all the numerical examples we had tried. On the other hand, we can utilize this insight to reduce the size of candidate points for constructing the optimal sampling time sequence by using exchange algorithms. This idea will be further elaborated in the next section.

Theorem 3.3 *Let* $\mathbf{M}$ *be the information matrix corresponding to a B-spline basis matrix* $\mathbf{B}$. *Suppose this B-spline system has its interior knots equidistantly placed between the two ends of the dynamic variable, then optimal interior sampling times must be symmetrically located between 0 and 1.*

With uniformly spaced internal knots, it is realized that a basis function of B-spline are symmetric to another basis function or itself. Using the Cauchy's expansion, it can be shown that if the time t, $t < 0.5$, is included in the optimal sampling sequence, then $1 - t$ must also appear in the sequence. Assume $\mathbf{b}_1$ and $\mathbf{b}_2$ are the vectors that correspond to the sampling time t and $1-t$, respectively. If $\mathbf{b_1}$ is a row vector to be augmented to $\mathbf{B}$, the new information matrix can be calculated as $\mathbf{M}+\mathbf{M}_1^d$, where $\mathbf{M}_1^d = \mathbf{b}_1^T\mathbf{b}_1$. Matrix $\mathbf{M}_1^d$ is a sparse matrix with a block of nonzero elements. This block is similar to the nonzero block in $\mathbf{M}_2^d$ calculated by $\mathbf{b}_2^T\mathbf{b}_2$. This similarity, between $\mathbf{M_1^d}$ and $\mathbf{M_2^d}$, is caused by the symmetrical behavior of bases due to uniformly spaced internal knots. As a result, sampling at t or $1-t$ has similar impact on the information matrix. Therefore, if one of them appear in the optimal sequence, the other one must also appear.

4. Algorithms

Finding the optimal sampling times of dynamic responses is a unique problem that would not be seen in the experiments with static responses. Sampling is required when there is a high cost associated with response measurement. Gaffke and Heiligers [10] presented the D-optimal designs for B-spline regression models and their designs were taking the approximate design form, which considers the design space to be continuous. This relaxation enables statisticians to find an explicit formula for the optimal solution, but its solution may not be feasible in practice, because the weight values of design points in an approximate design may not become integers for a given sample size. The exact designs that are obtained from exchange algorithms are considered in this paper.

4.1 Algorithm for finding D-optimal sampling times

Properties of an optimal $\mathbf{B}$ matrix are discussed in the previous section and these properties can be utilized to develop a deterministic search algorithm for finding the D-optimal sampling plan. Similar to PEA, the proposed algorithm requires a set of candidate points. Each row of matrix $\mathbf{B}$ (the design matrix) corresponds to a sampling time; i.e., for a time t there is a row vector $[b_1\ b_2\ ...\ b_N]$. Define an objective function to be

$$obj(t) := \max\{b_i^2\} - \lambda \sum_i \sum_{j>i} b_i b_j \tag{15}$$

We discretize the dynamic variable from 0 to 1 to give a list of t values. Then, with the list of $obj(t)$ values we find all local maxima and save their corresponding t's to the candidate set.

Parameter λ in Eq. (15) is a regularization parameter. This parameter eventually controls the trade-off between achieving a large increase in the diagonal element of information matrix and a decrease in the non-diagonal elements. The optimal λ value can be found by examining the determinants of information matrix versus different λ values, as shown in an example later. However, we can also preset several different λ values and create a larger set of candidate points to be used in the exchange algorithm.

Starting from a random initial design where sampling times are randomly assigned between 0 and 1, our algorithm replaces these sampling times by the times in the candidate set one by one. At each iteration, the Fedorov delta function will be evaluated for assessing the improvement in the determinant of information matrix when a current sampling time is replaced by a candidate sampling time. (For the Fedorov delta function, please refer to [28] and [32].) The iteration terminates when there is no more replacement that can increase the determinant of information matrix.

Algorithm 1 A New Approach for Finding Optimal Sampling Times

procedure
    Generate B-spline basis functions with order-m and n internal knots
    Generate the candidate set C; $C \leftarrow \arg(\max obj(t))$
    Generate the initial design matrix
    $i \leftarrow 1$
    while $\delta^* \geq e$ **do**
        for $j \in C$ **do**
            $\delta_j \leftarrow$ delta function of replacing the current sampling point by the jth candidate point.
        $\delta^* \leftarrow \max \delta_j$; $t_i \leftarrow$ the candidate point with $\max \delta_j$
        $i \leftarrow i + 1$.
        if $i >$ Number of rows in the design matrix **then**
            $i \leftarrow 1$.

The computation time and determinant value of the optimal design obtained by our algorithm are compared with those obtained from an exhaustive search over all possible sampling plans. Woods et al. [42] suggested to build the candidate set by choosing only sampling times around the locations where each basis function reaches its maximal value. Our approach further reduces this candidate set to only N candidate sampling times.

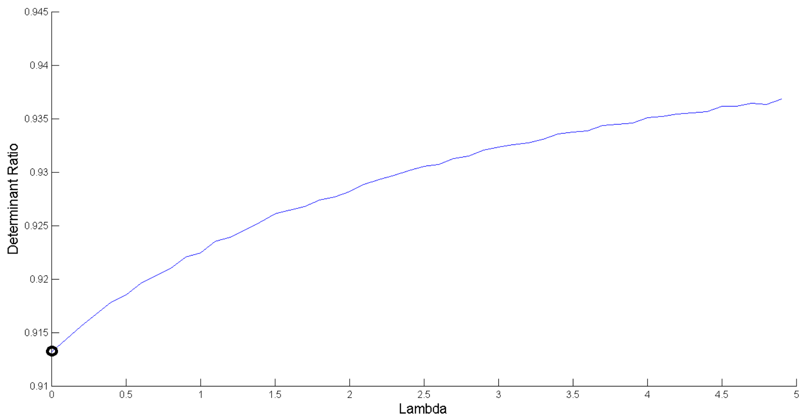

Figure 5: The D-efficiency of optimal design for different λ values. The experiment has 6 runs and the order-4 B-spline function has two internal knots at $\{0.3, 0.8\}$.

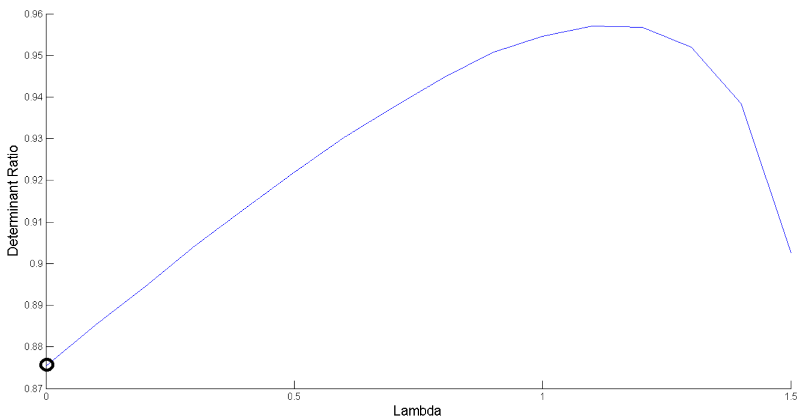

Figure 6: The D-efficiency of optimal design for different λ values. The experiment has 6 runs and the order-4 B-spline function has one internal knot at $\{0.1\}$.

Consider the examples in Figures 3 and 4. Varying the tuning parameter λ, we compare the D-efficiency of the optimal design from our algorithm to the one from exhaustive search. Figures 5 and 6 show that our algorithm is capable of reaching to the highest possible efficiency with a proper choice of λ. The computation time of our algorithm is much reduced from Woods et al. [42]. As to the first example (Figure 3), the average computation time of our algorithm is 0.06 seconds, comparing to 12 seconds by [42]. In addition, Kaishev [18] suggested to simply use the times where each basis function has its maximal value. The efficiency of this sampling plan is also marked by circle in the Figure 5 and Figure 6. It is clear that Kaishev's sampling plan is not optimal.

4.2 Robust sampling plans

The optimal sampling plan depends on the basis functions, thus the locations of interior knots, of B-spline system. The selection of knots in turn depends on the experimenter's knowledge of the shape of response curve. Therefore, the uncertainty existed in this prior knowledge at the experimental design stage requires the experimenter to consider a robust sampling plan. In the following example, five different basis systems with different locations of internal knots are used. Optimal sampling times for five systems are shown in Figure 7. Then, we apply the k-means clustering algorithm to cluster these optimal sampling times into k clusters, where k is less than the total number of sampling times determined by the experimenters. In the next step, the centroids of these clusters are stored in the candidate set and exchange algorithm is applied to construct the robust sampling plan, where the objective function is set as the median of D-efficiency for the all basis systems considered. Figure 8 shows the robust design for the five B-spline systems provided in Figure 7.

4.3 Optimal Design of Experiments with Dynamic Responses

In Section 2.2 we model the dynamic response system by a mixed effects model, so the D-optimal experimental design for such a system can obtained by applying the D-optimal criterion, Eq. (12). However, the design matrix $\mathbf{X}$ in Eq. (9) is a large matrix and it is constructed by horizontally stacking multiple functions of B-spline basis matrix $\mathbf{B}$, as explained for Eq. (9). Note that each row of $\mathbf{B}$ is required to sum to unity. As to the design matrix $\mathbf{X}$, this constraint needs to be checked multiple times for all of its submatrices. We have found that it is difficult to directly apply exchange algorithms on matrix $\mathbf{X}$. Therefore, in this section, we develop a two-step approach for finding the optimal design.

The first step is to find the optimal sampling times for a given B-spline basis system. This is the same as maximizing the information matrix of Model (5), $\mathbf{B}(\mathbf{t})^T\mathbf{B}(\mathbf{t})$. For example, consider a order-4 B-spline basis system with two interior knots at 0.3 and 0.6. These basis functions

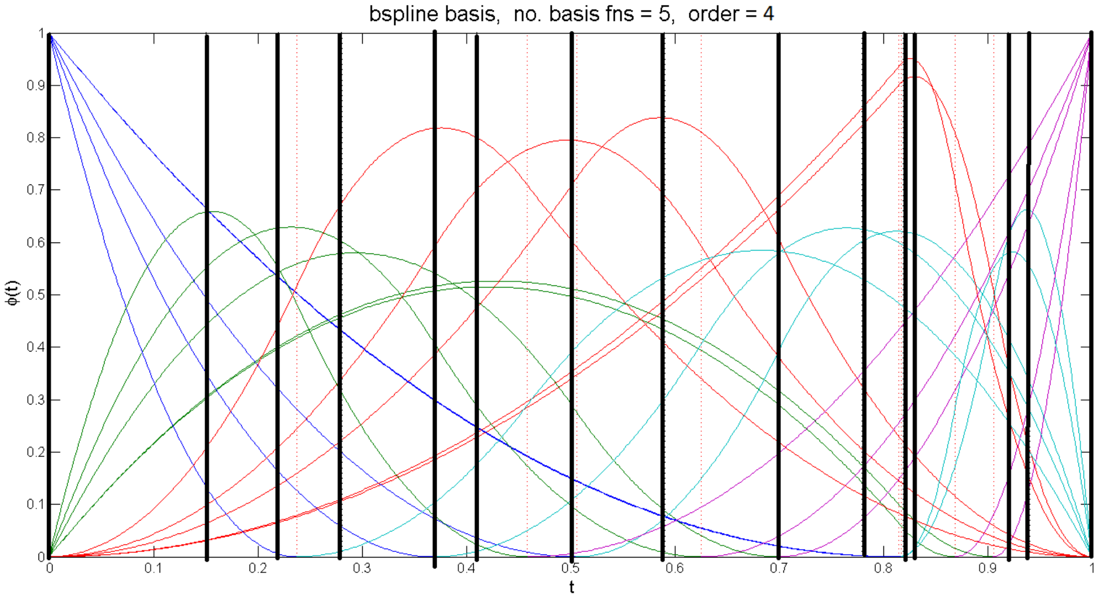

Figure 7: Five B-spline basis systems with order-3 and two internal knots at random locations. Optimal sampling times for different bases are depicted by solid bold lines, where the dotted lines indicates the location of the knots.

are plotted in Figure 9 and the optimal sampling times with different number of samples are listed in Table 1.

The number of bases of a B-spline system depends on the number of knots assigned to the system. Reducing the number of bases may result in losing modeling flexibility of some local behaviors of response curves under certain experimental conditions; while increasing the number of bases requires the experimenter to have more prior knowledge of the dynamic response and increases the complexity of experimental design.

After finding optimal sampling times, the second step is to find the optimal experimental

Table 1: Optimal sampling times for an order-4 B-spline basis system

Number of Samples	Optimal Sampling Times
6	{0,0.12,0.33,0.6,0.85,1}
7	{0,0.12,0.33,0.6,0.85,0.85,1}
8	{0,0.12,0.33,0.6,0.6,0.85,0.85,1}
9	{0,0.12,0.33,0.33,0.6,0.6,0.85,0.85,1}
10	{0,0.12,0.12,0.33,0.33,0.6,0.6,0.85,0.85,1}

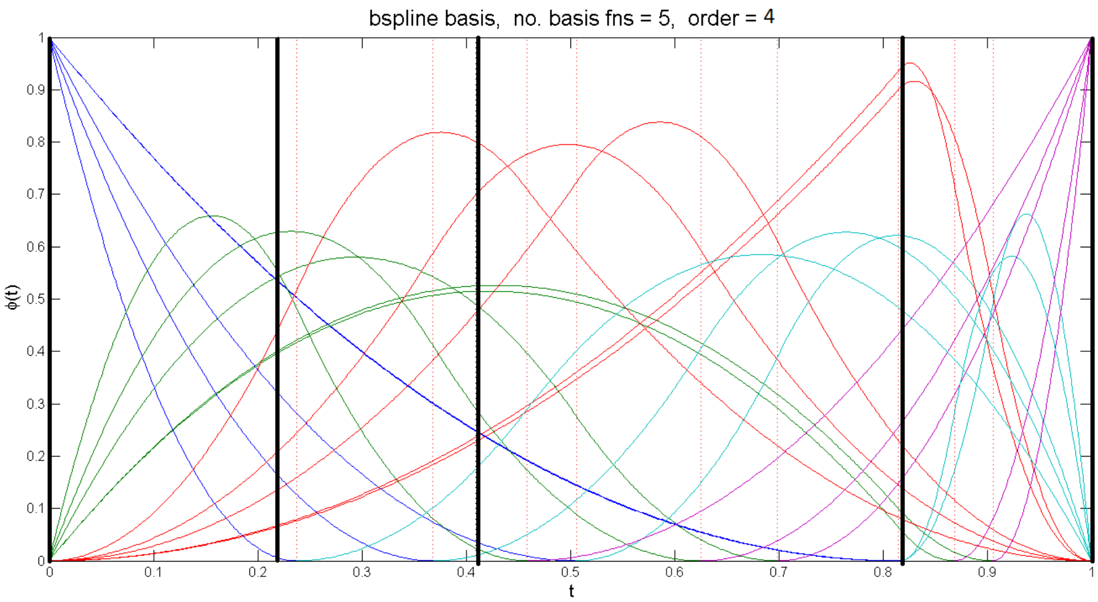

Figure 8: Robust D-optimal design for the 5 B-spline systems provided in Figure 7. Each sampling time has two replicates for an experiment with 10 sampling times.

condition for each experimental unit, i.e., the optimal $\mathbf{X}$ in Eq. (9). Note that $\mathbf{X} = (\mathbf{I_N} \otimes \mathbf{B})\mathbf{F}(\mathbf{x})$. With $\mathbf{B}$ is fixed, we applied the exchange algorithm to find the optimal $\mathbf{F}(\mathbf{x})$ to maximize the D-optimal design objective given by Eq. (12).

To compare this two-step approach to other methods, we consider the previous example of order-4 B-spline system with 3 experimental factors and 55 experimental units. The range of each factor is scaled to -1 to 1, so the design region is a cube. Beside of the two-step approach, we apply two other approaches – optimizing the D-objective, Eq. (12), with randomly chosen sampling times or uniformly spaced sampling times. The designs derived from these approaches are listed in Table 2. We varied the number of sampling times from 6 to 10. However, using the two-step approach, the selected experimental conditions are the same for any number of sampling times, so they are listed in one column. The numbers in each column of Table 2 are the number of experimental units assigned to the corresponding experimental conditions. The determinants of the information matrices of these designs are given in Table 3. One can see that the two-step approach is clearly superior than the other two approaches in terms of providing designs with larger determinant values of information matrix.

Table 2: Optimal experimental designs of an order-4 B-spline system with 3 experimental factors and 55 experimental units

	Sampling Strategies										
$\mathbf{x}$ (experimental conditions)	Two-step	Random-6	Random-7	Random-8	Random-9	Random-10	Equal-6	Equal-7	Equal-8	Equal-9	Equal-10
$\{-1,-1,-1\}$	14	11	14	14	14	11	14	13	12	14	14
$\{-1,-1,1\}$	13	5	10	11	5	5	13	11	4	12	13
$\{-1,1,-1\}$	14	8	12	13	8	8	14	14	8	13	14
$\{-1,1,1\}$	0	6	4	3	9	7	14	5	7	0	0
$\{1,-1,-1\}$	14	8	9	10	4	7	0	9	6	4	0
$\{1,-1,1\}$	0	5	2	1	6	6	0	0	6	0	0
$\{1,1,-1\}$	0	0	4	3	9	9	0	2	10	2	14
$\{1,1,1\}$	0	9	0	0	0	2	0	1	2	0	0

Table 3: Determinants of the information matrices of experimental designs derived from three approaches.

	Determinants for Sampling Strategies		
Number of Sampling Times	Optimal	Random	Equal
6	2.75E+17	1.02E+10	2.16E+16
7	1.42E+18	2.43E+13	4.41E+17
8	7.34E+18	3.28E+15	2.91E+18
9	3.74E+19	1.61E+16	1.17E+19
10	1.91E+20	1.37E+17	3.87E+19

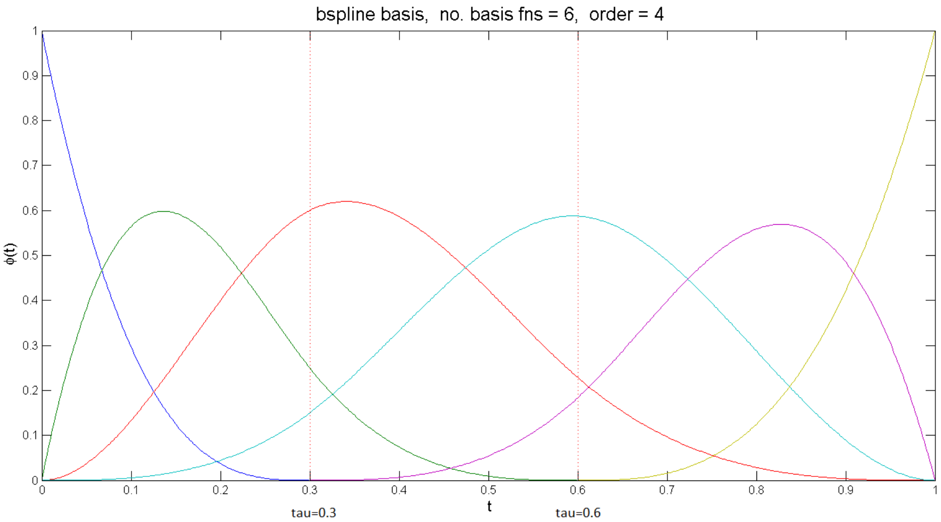

Figure 9: The order-4 B-spline bases system with interior knots located at $\{0.3, 0.6\}$.

5. An Industrial Case

In this section, we apply the two-step approach to find the optimal experimental designs for an engineering example in the literature. We compare them with the standard design and the engineer's suggested design. The standard design is obtained by uniformly placing sampling times combined with D-optimal design of experimental factors, while the engineer's suggested design is taken from the literature.

This example concerns with designing an electrical alternator (see Nair et al. [30]). The response variable is electric current. The dynamic variable is the revolution per minute (RPM) and it is sampled at $RPM = \{1375, 1500, 1750, 2000, 2500, 3500, 5000\}$ for 108 designed alternators (see Figure 10). After scaling the range of dynamic variable to [0, 1], we have these sampling points at $\{0, 0.03, 0.1, 0.17, 0.31, 0.58, 1\}$. Eight controllable factors and two noise factors are considered in this example.

We use an order-4 B-spline system to model the response profiles over RPM and place two interior knots at $\{0.3, 0.6\}$. Then, the optimal sampling times are located at {0, 0.12, 0.33, 0.6, 0.85, 0.85, 1}. The determinants of information matrices of the engineer suggested design in Nair et al. [30], the standard design, and the D-optimal design derived from the two-step approach are compared in Table 4. One can see that the determinant of design matrix of

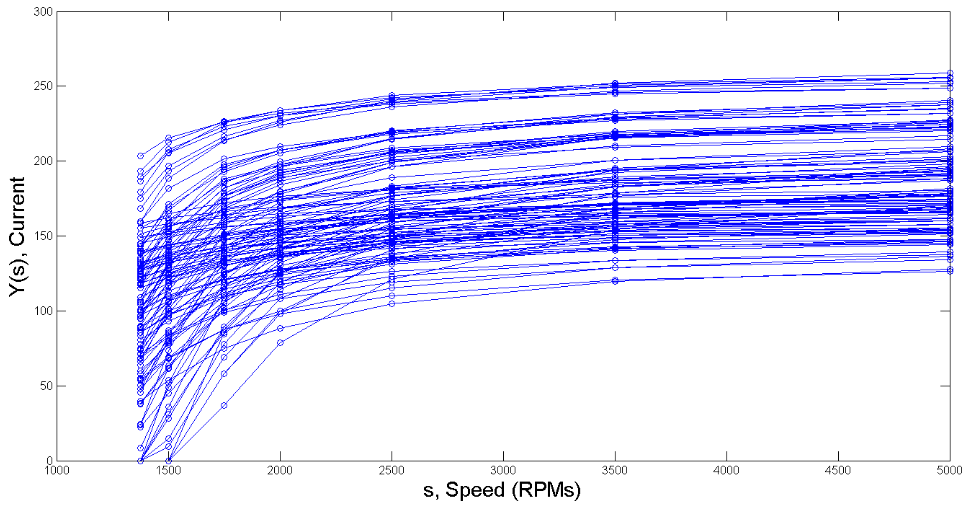

Figure 10: 108 profile curves derived from the experiments conducted for designing the electrical alternator. The electric current values are marked by circles and they are connected by straight lines.

Table 4: Determinants of the information matrix from the optimal design, standard design, and engineer suggested design

Design	Determinant
Optimal Design	$6.04E + 90$
Standard Design	$1.30E + 89$
Engineer Suggested Design	$4.08E + 48$

optimal design is much larger than the standard design, while the engineer suggested design is the worst one among them.

6. Conclusions

The dynamic response system studied in this paper generates response curves that can be modeled as functions of a time variable or another dynamic variable. The features of these response curves and their interactions with other experimental factors are of interest to experimenters, thus it requires new experimental design methods for exploring such a system efficiently.

The statistical models for quantifying such dynamic responses are explored in this paper. We resort to B-spline functions to model dynamic responses given its flexibility, yet affinity to traditional linear models. With the parameters in B-splines being further defined as functions of other controllable variables, it is shown that the entire model becomes a mixed effects linear model, thus allowing the use of linear design theory. For a simple spline function, we demonstrate several theorems that can assist in constructing an efficient sampling plan, which is good at revealing the features of response curves. When consider other controllable variables, we propose a two-step approach for finding both the optimal experimental conditions and optimal sampling points. An exchange algorithm is proposed for finding the D-optimal design. Finally, we employ an industrial example to demonstrate the superior performance of our approach. As described in the introduction section, dynamic responses are very common from engineering systems; however, experimental designs for such systems have not been researched adequately. This paper is only the beginning of a research effort to explore this new topic. In future we plan to research other types of dynamic response analysis methods, such as functional principal component analysis that can model the dynamics in both input variables and response variables, simultaneously.

Acknowledgement

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Appendix

First, denote the determinant of a $n \times n$ matrix $\mathbf{A}$ by $|\mathbf{A}|$. Let S_{ij} be the determinant of a submatrix of $\mathbf{A}$, which is obtained from $\mathbf{A}$ by deleting row i and column j. S_{ij} is also called the first minor of $|\mathbf{A}|$. Denote the cofactor of an element a_{ij} in $\mathbf{A}$ as A_{ij} and

$$A_{ij} = (-1)^{i+j} S_{ij}.$$

It can be shown that

$$|\mathbf{A}| = \sum_{k=1}^{n} a_{ik} A_{ik}.$$

The cofactor matrix $\mathbf{C}(\mathbf{A})$ is a $n \times n$ matrix with elements of cofactor A_{ij}. In addition, define $S_{i_1 i_2; j_1 j_2}$ be the second minor of $|\mathbf{A}|$. It is the determinant of a submatrix of $\mathbf{A}$, which is obtained from matrix $\mathbf{A}$ by rejecting rows i_1, i_2 and columns j_1, j_2. It is also known as a rejecter minor. Then, the second cofactor of $|\mathbf{A}|$, denoted by $A_{i_1 i_2; j_1 j_2}$, is defined as a signed second reject minor such as

$$A_{i_1 i_2; j_1 j_2} = (-1)^{i_1 + i_2 + j_1 + j_2} S_{i_1 i_2; j_1 j_2}.$$

With these definitions, we can proceed to prove Theorem 3.1. First, the following lamma is required.

Lemma 6.1 *Let matrix* $\mathbf{A}$ *be a symmetric positive definite matrix, then its cofactor matrix* $\mathbf{C}(\mathbf{A})$ *is also positive definite.*

Proof: Because $\mathbf{A}$ is symmetric and positive definite, its determinant $|\mathbf{A}| > 0$ and its inverse $\mathbf{A}^{-1}$, if exists, is positive definite too. For a symmetric matrix, its cofactor matrix must be symmetric too and it is the same as its adjugate matrix, which is the transpose of cofactor matrix. It is also known that the adjugate matrix equals to $\frac{1}{|\mathbf{A}|}\mathbf{A}^{-1}$. Therefore, the cofactor matrix $\mathbf{C}(\mathbf{A})$ is also positive definite.

Proof of Theorem 3.1: Let M_{ij} be the cofactor of element m_{ij} in matrix $\mathbf{M}$. Consider the first diagonal element m_{11} of the positive definite symmetric matrix $\mathbf{M}$. By the Cauchy's expansion (see Theorem 3.11 in Vein and Dale [38]) its determinant is given by

$$|\mathbf{M}| = m_{11}M_{11} - \omega_1,$$

where $\omega_1 = \sum_{i=1}^{n}\sum_{j=1}^{n} m_{1i}m_{j1}M_{1i;j1}$ and $M_{1i;j1}$ is a second cofactor, which is obtained by the signed determinant of rejecter matrix. This rejecter matrix is obtained from $\mathbf{M}$ by rejecting rows $1, i$ and columns $j, 1$. As m_{1i} and m_{j1} are numerical variables and $m_{1i} = m_{i1}$, $m_{j1} = m_{1j}$ due to symmetry, ω_1 is in fact a quadratic form of $n-1$ variables, $m_{12}, m_{13}, ..., m_{1n}$, and their corresponding cofectors. That is, let $\mathbf{m}_1 = [m_{12}, m_{13}, ..., m_{1n}]^T$ and $\mathbf{C}(\mathbf{R}_{11})$ be the cofactor matrix of the rejector $\mathbf{R}_{11}$. Note that $\mathbf{R}_{11}$ is a principal submatrix of $\mathbf{M}$ and the cofactor $M_{11} = |\mathbf{R}_{11}|$. Hence, in the quadratic form, $\omega_1 = \mathbf{m}_1^T\mathbf{C}(\mathbf{R}_{11})\mathbf{m}_1$. Now, because $\mathbf{M}$ is positive definite, its principle submatrices are positive definite too. Following Lemma 6.1, $\mathbf{C}(\mathbf{R}_{11})$ is positive definite. Consequently, ω_1 is greater than 0, except when $\mathbf{m}_1 = \mathbf{0}$. The Cauchy's expansion can be used again for expanding M_{11}, which is equivalent to the determinant of rejecter matrix $\mathbf{R}_{11}$. Thus,

$$M_{11} = m_{22}M_{12;12} - \omega_2$$

and

$$|\mathbf{M}| = m_{11}m_{22}M_{12;12} - m_{11}\omega_2 - \omega_1.$$

Here, again, ω_2 is greater than 0, except when $\mathbf{m}_2 = \mathbf{0}$. Continuing the expansion, we will have

$$|\mathbf{M}| = \prod_{i=1}^{n} m_{ii} - \omega_T,$$

where $\omega_T = \omega_1 + m_{11}\omega_2 + m_{11}m_{22}\omega_3 + ... + m_{11}m_{22}...m_{nn}\omega_n$ and it is non-negative.