Optimal designs for experiments for scalar-on-function linear models

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The aim of this work is to extend the usual optimal experimental design paradigm to experiments where the settings of one or more factors are functions. Such factors are known as profile factors, or as dynamic factors. For these new experiments, a design consists of combinations of functions for each run of the experiment. After briefly introducing the class of profile factors, basis functions are described with primary focus given on the B-spline basis system, due to its computational efficiency and useful properties. Basis function expansions are applied to a functional linear model consisting of profile factors, reducing the problem to an optimisation of basis coefficients. The methodology developed comprises special cases, including combinations of profile and non-functional factors, interactions, and polynomial effects. The method is finally applied to an experimental design problem in a Biopharmaceutical study that is performed using the Ambr250 modular bioreactor.

Keywords: Basis functions; Design of Experiments; Functional Linear Model; Profile Factors.

1 Introduction

In science and engineering, an increasing number of experiments involve the investigation of the relationship between a response and profile factors, i.e. variables whose values can be varied as a function, usually of time, within a single run of an experiment. A common example of a profile variable is temperature, being varied monotonically or as a step function through the run. The statistical design problem then becomes choosing suitable functions that determine how each profile factor varies during each run. For ease of exposition, throughout this paper we shall assume time $t \in [0, T]$ is the continuous single input to profile factors. The methods extend naturally to situations where there are profile factors with multiple inputs, e.g. spatio-temporal studies.

Design of experiments (DOE) is a well-established research topic in the Statistics literature for more than 100 years. Similarly, statistical modelling with functional data is well established in the statistics literature, see Ramsay and Silverman (2005). However, the design of experiments for models that involve profile factors has received much less attention, with two main approaches being proposed: adaptation of response surface methods using dimension-reduction techniques (Georgakis (2013), Roche (2015), Klebanov and Georgakis (2016), and Roche (2018)) and optimal design for dynamic models, typically derived from differential equations (Balsa-Canto, Rodriguez-Fernandez, and Banga (2007), and Uciński and Bogacka (2007)).

We develop a methodology that is related to the response surface approach, to find optimal functions for profile factors assuming a scalar-on-function linear model. In the best of our knowledge, there is no work addressing functional empirical models depending on multiple profile factors, where the parameters requiring estimation are themselves functions of time. Our approach leverage the power of standard linear model optimal design methodology and its flexibility allows designs to be obtained for various different scenarios and using different optimality criteria.

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This work is motivated by a Biopharmaceutical study and an experiment performed using the Ambr250 modular bioreactor system for process development. The study aims to investigate the titre content, to monitor and optimise the cell growth. As indicated by Tai, Leung, and Nayar (2015), the importance of the use of design of experiments with the Ambr250 bioreactor system is to allow a more efficient exploration of the design space. They mentioned that traditionally scientist employed resolution III and IV fractional-factorial designs for the initial screening studies to identify significant process parameters. Tai et al. (2015) used a 10-factor definitive screening designs (DSD) for experiments in the 24-bioreactor Ambr250 system.

However, during experimentation using the Ambr250, other than scalar factors, we can control a variety of factors as a function of time, including but not limited to, temperature and feed rate. Several scientists in the literature mentioned that considering factors that vary with respect to time could be beneficial; see Yoon, Kim, and Lee (2003), Trummer et al. (2006), and Rameez et al. (2014). In context, Yoon et al. (2003) indicated the importance of changing temperature, and discussed that lowering the values of temperature dynamically promoted high cell concentration. Trummer et al. (2006) found that a maximisation of cell growth can be obtained by varying temperature using a biphasic process strategy. In a more recent work, Rameez et al. (2014) concluded that a downward shift in temperature caused an increase in the concentration of the cell. Additionally, Lu et al. (2013) mentioned that typically fixed bolus feeding is employed for cell cultures and continued to discuss that there is significant improvement in the titre content via a dynamic feeding strategy. The application of a real experiment in the Ambr250 presented in this work had four factors; three scalar factor which are initial viable cell concentration, pH, and temperature, and one profile factor which is feed volume.

The next section, Section 2, introduces the functional linear model. The challenges confronted with this model type are defined, and the use of basis functions to restrict the function space of functions is discussed. In Section 3 a new methodology for design of experiments that depend on profile factors is developed. The methodology is developed in the frequentist and the Bayesian framework, and the connection between the two approaches is discussed. An illustrative example to demonstrate the methodology and investigate the choice of basis and basis functions is given in Section 4. The final section, Section 5, contains an application of a real experiment in the Ambr250 that depends on combination of scalar and profile factors.

2 Introduction to the functional linear model

An experiment is assumed to take place from time 0 to time $T$, i.e., $0 \leq t \leq T$. The experiment is assumed to consist of $n$ runs. The $i^{th}$ run of the experiment involves specifying the controllable functions of the profile factors to measure the scalar responses at time $T$. A standard model in literature to model the relationship between the scalar response and profile factors, is the functional linear model. The functional linear model was first introduced by Ramsay (1991) and later discussed by Hastie and Mallows (1993) as an additive model of main effects of profile factors; see the first part of the model in (1). Quadratic effects of the profile factors are described through the quadratic functional linear model, which for a total of $J$ profile factors at the $i^{th}$ run of the experiment is
defined as,

\[ y_i = \int_0^T x_i^T(t) \beta(t) \, dt + \sum_{j=1}^J \int_0^T \int_0^T x_{ij}(t_1) x_{ij}(t_2) \beta_j(t_1, t_2) \, dt_1 dt_2 + \epsilon_i, \]

\[ i = 1, \ldots, n, \quad t, t_1, t_2 \in [0, T], \]

with \( y_i \) the response at the \( i \)th run of the experiment, and \( \epsilon_i \) the independent and identically distributed errors with mean zero and variance \( \sigma^2 \). The \( J \times 1 \) vector \( x_i(t) \) represents the functions of the profile factors at the \( i \)th run of the experiment,

\[ x_i^T(t) = (x_{i1}(t) \ldots x_{ij}(t)) , \quad i = 1, \ldots, n, \]

with each \( x_{ij}(t), i = 1, \ldots, n, j = 1, \ldots, J \), the function of the \( j \)th profile factor at the \( i \)th run of the experiment. The \( J \times 1 \) vector \( \beta(t) \) represents the vector of the unknown functional parameters,

\[ \beta^T(t) = (\beta_1(t) \ldots \beta_J(t)), \]

with each functional parameter \( \beta_j(t) : [0, T] \to \mathbb{R}, j = 1, \ldots, J \) an unknown function of time \( 0 \leq t \leq T \). The first part of the model in (1) is the linear additive component of the main effects of the profile factors, and the second part is the quadratic component that involves the quadratic polynomial of the functions of the profile factors and square integrable bivariate parameter functions \( \beta(t_1, t_2) \). A higher order functional linear model, with up to the \( k \)th order polynomial of the functions of the profile factors, is given in Yao and Muller (2010). The functional linear model with interactions of profile factors is constructed in a similar way; see Usset, Staicu, and Maity (2016) for a functional linear model that involves the \( 2^{nd} \) order interactions of the profile factors involved in the model.

2.1 Restrictions through the use of basis functions

The first problem arising under the functional linear model is the estimation of the functional parameters. The functional linear model in (1) can be viewed as essentially having to estimate an infinite number of unknown parameters. This is because functions in general, and subsequently the functional parameters, are infinite dimensional objects. However, the experiment only returns a finite number of observed responses. As a result, the system is under-determined; it consists of fewer equations than unknown parameters. Thus, there exists an infinite number of solutions for the unknown parameters that fit perfectly to the observed responses. To overcome this problem, the function space of the functional parameters is restricted via basis function expansions; see page 44 in Ramsay (2005). For univariate parameter functions, the basis function expansions are defined as,

\[ \beta_j(t) = \sum_{l=1}^{n_{\beta,j}} \theta_{jl} b_{jl}(t) = b_j^T(t) \theta_j, \quad j = 1, \ldots, J, \]

where the functions \( b_j^T(t) = [b_{j1}(t), \ldots, b_{qn_{\beta,j}}(t)] \) are known basis functions and the vector \( \theta_j^T = (\theta_{j1}, \ldots, \theta_{jn_{\beta,j}}) \) is a vector of unknown coefficients. The special case of a scalar parameter \( \beta_j \) or the
constant parameter for the intercept is represented through a single basis function $n_{\beta,j} = 1$ which is constantly equal to one, i.e., $b_{j1}(t) = 1$. As a result, the problem of estimating the unknown functions of the parameters has been reduced to the problem of estimating $\sum_{j=1}^{J} n_{\beta,j}$ coefficients.

The bivariate functional parameters are expanded through the bivariate tensor product of univariate basis. The bivariate tensor product basis for $t_1, t_2$ is defined over the 2-dimensional region $[0, T] \times [0, T]$, and thus, the bivariate function can be represented as a linear combination of the basis functions of two basis, as in Fuchs (2015),

$$
\beta_j(t_1, t_2) = \sum_{l=1}^{n_{\beta,k}} \sum_{m=1}^{n_{\beta,j}} \theta_{lm} b_j(t_1) b_m(t_2)
= [b_j(t_1) \otimes b_j(t_2)]^\top \text{vec}(\theta_j),
$$

with $b_j(t) = [b_{j1}(t), \ldots, b_{jn_{\beta,j}}(t)]$ a $n_{\beta,j} \times 1$ vector of known basis functions, and $\text{vec}(\theta_j)$ the $n_{\beta,j}^2 \times 1$ vectorisation of the $n_{\beta,j} \times n_{\beta,j}$ matrix $\theta_j$. Higher order parameter functions are similarly expanded through the full tensor product of univariate basis, i.e., the basis expansion of $k$-variate parameter function can be represented through the same approach, by $k$ individual basis; see De Boor (1978, page 293). For bivariate functional parameters, the number of basis functions, and hence the number of parameters we need to estimate increases. For instance, the number of basis functions goes up with the square of the size of each individual basis. For this reason, a simplified form of the model to restrict the parameter functions is considered instead; see Yao and Müller (2010) and Morris (2015). The restriction in the parameter functions can be achieved through properties of the Dirac delta. The Dirac delta is defined as a function on the real line that is always zero, except when at the origin; see Balakrishnan (2003). A property of the Dirac delta is that for a general function $g(t)$,

$$
\int_0^T g(t) \delta(t) \, dt = g(0),
$$

with $\delta(\cdot)$ the Dirac delta function; see Balakrishnan (2003). Without loss of generality, expanding the property for a quadratic parameter function through shifting the Dirac delta function along the axis gives,

$$
\int_0^T g(t_1, t_2) \delta(t_2 - t_1) \, dt_2 = g(t_1, t_1).
$$

By the property of the Dirac delta discussed above, the double integral depending on the quadratic parameter function is restricted to,

$$
\int_0^T \int_0^T x_1(t_1) x_2(t_2) \beta(t_1, t_2) \delta(t_2 - t_1) \, dt_1 dt_2
= \int_0^T x_1(t_1) x_2(t_1) \beta(t_1) \, dt_1,
$$

for $\beta(t_1) = \beta(t_1, t_1)$, as the second argument becomes redundant. Thus, the variation of the functional quadratic model is modelled through integrating the quadratic term on a single time indexing. Following the latter, the functional linear model can be simplified to a single time integral model,

$$
y_i = \int_0^T f^T(x_i(t)) \beta(t) \, dt + \epsilon_i, \quad i = 1, \ldots, n.
$$
for \( \boldsymbol{x}_i(t) \) and \( \beta(t) \) as in (2) and (3) respectively. The structure of the model, i.e., the functions of interest including the main effects, interactions and polynomials, is specified through the \( Q \times 1 \) functional of the functions of the profile factors \( f^T(\boldsymbol{x}_i(t)) \) with \( Q \) the total number of terms in the model,

\[
\begin{align*}
    f^T(\boldsymbol{x}_i(t)) &= \left( f_1(\boldsymbol{x}_i(t)) \cdots f_Q(\boldsymbol{x}_i(t)) \right),
    \quad i = 1, \ldots, n.
\end{align*}
\]  

(7)

An intercept is similarly incorporated in the model through the function \( f_1(\boldsymbol{x}_i(t)) \). If the intercept is included in the model, the first component of the vector of the function \( f^T(\boldsymbol{x}_i(t)) \) is 1, i.e., \( f_1(\boldsymbol{x}_i(t)) = 1 \).

The second problem arising is the design of experiments problem to appropriately choose the functions \( \boldsymbol{x}_i(t) \), \( i = 1, \ldots, n \). Choosing the best functions is essential to achieve optimal conditions for the experiment. The function space for each profile factor, may be very general, or may be restricted to particular classes of functions, including polynomials to a certain degree or step functions with particular break points, based on the operation of the experiments. Inference from a given experiment requires some restrictions on the function space of the profile factors, also achieved via basis function expansions,

\[
    x_{ij}(t) = \sum_{l=1}^{n_{x,j}} \gamma_{ijl} c_{jl}(t), \quad i = 1, \ldots, n, j = 1, \ldots, J.
\]  

(8)

The basis expansion for each profile factor can be written in vector form as, \( \boldsymbol{x}_{ij}(t) = \Gamma_j \boldsymbol{c}_j(t) \), with \( \boldsymbol{x}_j \) the function of the \( j^{th} \) profile factor in every run of the experiment, known basis functions \( \boldsymbol{c}_j(t) = [c_{j1}(t), \ldots, c_{jn_{x,j}}(t)] \), and \( \Gamma_j \) a \( n \times n_{x,j} \) coefficient matrix with \( \gamma_{ijl} \) the \( il^{th} \) entry, \( i = 1, \ldots, n, j = 1, \ldots, J, l = 1, \ldots, n_{x,j} \). In addition, the basis expansion can handle the special case of scalar factors. A scalar factor \( x_{ij} \) is represented through a single basis function \( n_{x,j} = 1 \) which is constantly equal to one, i.e., \( c_{j1}(t) = 1 \). After that, \( x_{ij} = \gamma_{ij1} \) is a single value that needs to be specified in every run of the experiment.

3 DOE methodology development

Bringing together the basis expansions from (4) and (8) and working in the matrix form of the functional linear model from (7) results in an extended form of the linear model,

\[
    \mathbf{y} = \int_0^T f^T(\mathbf{X}(t)) \mathbf{\beta}(t) \, dt + \mathbf{\epsilon} = \int_0^T f^T(\mathbf{X}(t)) \mathbf{b}^T(t) \, dt + \mathbf{\epsilon} = \mathbf{Z}\mathbf{\theta} + \mathbf{\epsilon},
\]  

(9)

with \( \mathbf{y}^T = (y_1, \ldots, y_n) \) the \( n \times 1 \) vector of responses, \( \mathbf{Z} \) the \( n \times \sum_{q=1}^Q n_{\beta,q} \) model matrix, \( \mathbf{\theta} \) the \( \sum_{q=1}^Q n_{\beta,q} \times 1 \) vector of unknown parameters from the expansion of the functional parameters, and \( \mathbf{\epsilon}^T = (\epsilon_1, \ldots, \epsilon_n) \) the \( n \times 1 \) vector of independent error terms with mean zero and variance-covariance \( \sigma^2 \mathbf{I}_n \). The matrix \( \mathbf{X}(t) \) is a matrix of dimensions \( n \times J \) with the \( ij^{th} \) entry containing the function.
of the $j^{th}$ profile factor at the $i^{th}$ run of the experiment, $i = 1, \ldots, n, j = 1, \ldots, J$. Thus, every row of $X(t)$ is the vector $x_i^T(t)$. Equivalently, the $j^{th}$ column of $X(t)$ is the vector $x_j(t), j = 1, \ldots, J,$ that represents the function of the $j^{th}$ profile factor in every run of the experiment such that,

$$X(t) = \left(x_1^T(t) \quad \ldots \quad x_n^T(t)\right)^T = \left(x_1(t) \quad \ldots \quad x_J(t)\right) = \left(\Gamma_1 c_1(t) \quad \ldots \quad \Gamma_J c_J(t)\right).$$  

(10)

The function $f^T(X(t))$ is an $n \times Q$ matrix acting row-wise on $X(t)$, with the $q^{th}$ column representing the $q^{th}$ term in the model, $q = 1, \ldots, Q$. In other words, the $iq^{th}$ entry of $f^T(X(t))$ is a function of the profile factors, specified by $f_q$, in the $i^{th}$ run of the experiment,

$$f^T(X(t)) = \left(f_1(X(t)) \quad \ldots \quad f_Q(X(t))\right).$$  

(11)

If the $q^{th}$ function represents the intercept, then $f_q(X(t)) = 1_n$, with $1_n$ being the $n \times 1$ vector of 1’s. Additionally, the matrix $b(t)$ is a $\sum_{q=1}^{Q} n_{\beta,q} \times Q$ block matrix containing the known basis functions $b_q(t)$ from the expansion of the functional parameters in (4),

$$b(t) = \begin{pmatrix} 
    b_1(t) & 0 & \ldots & 0 \\
    0 & b_2(t) & \ldots & 0 \\
    \vdots & \vdots & \ddots & \vdots \\
    0 & 0 & \ldots & b_Q(t) 
\end{pmatrix}.$$  

(12)

The model matrix $Z$ is partitioned in $Q$ column blocks, with the $q^{th}$ column block a $n \times n_{\beta,q}$ matrix $Z_{q}$ which is the solution to an integral of the form,

$$Z_q = \int_0^T f_q(X(t)) \ b_q^T(t) \ dt = \int_0^T f_q \left(\Gamma_1 c_1(t) \quad \ldots \quad \Gamma_J c_J(t)\right) \ b_q^T(t) \ dt,$$

$q = 1, \ldots, Q.$  

(13)

If the $q^{th}$ partition of the model matrix corresponds to the main effect of a profile factor, the column block is the solution to an integral of the form,

$$Z_q = \int_0^T x_j(t) \ b_j^T(t) \ dt = \Gamma_j \int_0^T c_j(t) \ b_j^T(t) \ dt, \quad j = 1, \ldots, J.$$  

(14)

However, if the $q^{th}$ partition of the model matrix corresponds to the $K$-order effect of a profile factor or to the $K$-way interaction of profile factors, the column block is the solution to an integral of the
can also be expressed as,
\[
Z_q = \int_0^T f_q(X(t)) \ b_q^T(t) \ dt \\
= \int_0^T f_q \left( x_{j_1}(t) \ \cdots \ x_{j_K}(t) \right) \ b_q^T(t) \ dt \\
= \int_0^T (\Gamma_{j_1} c_{j_1}(t) \ \cdots \ \Gamma_{j_K} c_{j_K}(t) ) \ b_q^T(t) \ dt, \\
q = J + 1, \ldots, Q,
\] (15)

with $\odot$ the Hadamard product, $f_q(X(t))$ the $q^{th}$ column of $f^T(X(t))$, and $b_q(t)$ the basis functions from the expansion of the $q^{th}$ functional parameter. The Hadamard product of the functions of the profile factors $x_{j_1}(t) \ \cdots \ x_{j_K}(t)$ represent a $K$-way interaction of the functions of the profile factors $x_{j_1}(t), \ldots, x_{j_K}(t)$ if $j_1 \neq \ldots \neq j_K$, or a $K$-order effect if $j_1 = \cdots = j_K$. The partition in (15) can also be expressed as,
\[
Z_q = \Gamma_{j_1 \cdots j_K} \int_0^T (c_{j_1}(t) \ \otimes \ \cdots \ \otimes \ c_{j_K}(t) ) \ b_q^T(t) \ dt \\
= \Gamma_{j_1 \cdots j_K} \int_0^T c_{j_1 \cdots j_K}(t) \ b_q^T(t) \ dt, \\
q = J + 1, \ldots, Q,
\] (16)

with $\otimes$ the Kronecker product. The matrix $\Gamma_{j_1 \cdots j_K}$ is the $n \times \prod_{k=1}^K n_{x,j_k}$ coefficient matrix for which each column is the Hadamard product of the form,
\[
\text{col}_{l_1}(\Gamma_{j_1}) \ \odot \ \cdots \ \odot \ \text{col}_{l_K}(\Gamma_{j_K}),
\]

with $\text{col}_l(\Gamma)$ the $l^{th}$ column of the matrix $\Gamma$, and $l_1, \ldots, l_K$ arbitrary choices of column index for matrices $\Gamma_{j_1}, \ldots, \Gamma_{j_K}$, respectively. The complete set of columns $\Gamma_{j_1}, \ldots, \Gamma_{j_K}$ is formed by considering all possible choices of $l_1, \ldots, l_K$, arranged in lexicographical order. The vector $c_{j_1 \cdots j_K}(t)$ is the $\prod_{k=1}^K n_{x,j_k} \times 1$ vector of Kronecker products of the profile factor basis functions,
\[
c_{j_1 \cdots j_K}(t) = c_{j_1}(t) \ \otimes \ \cdots \ \otimes \ c_{j_K}(t),
\]

with each entry the product of $j_K$ basis functions, one for each different profile factor, and all possible combinations of choices are considered in a way similar to the construction of the columns of $\Gamma_{j_1 \cdots j_K}$.

### 3.1 Frequentist approach

The functional linear model in equation (9) is an extension of the traditional linear model, with $Z$ the model matrix and $\theta$ the unknown coefficients, with dimensions of $Z$ and $\theta^T$ being $n \times \sum_{q=1}^Q n_{\beta,q}$ and $1 \times \sum_{q=1}^Q n_{\beta,q}$, respectively. An estimator of $\theta$ can be found by the ordinary least squares method which minimises the residual sum of squares,
\[
\text{RSS} = (y - Z\theta)^T(y - Z\theta).
\] (17)
After that, the parameter estimator $\hat{\theta}$ and the variance-covariance matrix of the parameter estimator are respectively defined as,

$$\hat{\theta} = (Z^T Z)^{-1} Z^T y.$$  \hfill (18)

$$\text{Var}(\hat{\theta}) = \text{Var}[(Z^T Z)^{-1} Z^T y] = \sigma^2(Z^T Z)^{-1}. \hfill (19)$$

However, the choice of basis functions is usually difficult, i.e., for a spline of fixed degree, it is equivalent to choosing the number and location of the knots. An alternatively approach is to use a roughness penalty to enforce smoothing by penalising the complexity of functions and the equations can be regularised via the addition of a smoothing penalty added on the residual sum of squares. As a result this reduces the problem to choosing a single smoothing parameter $\lambda$ that controls the trade-off between fit and smoothness. Hence, the parameter estimator is estimated by the penalised residual sum of square; see Ramsay (2005),

$$PRSS = (y - Z\theta)^T (y - Z\theta) + \lambda \theta^T R_0 \theta, \hfill (20)$$

where $\lambda > 0$ is a scalar smoothing parameter and $R_0$ is a $\sum_{q=1}^{Q} n_{\beta,q} \times \sum_{q=1}^{Q} n_{\beta,q}$ block diagonal matrix, representing the roughness penalties. Under the roughness penalty approach, the parameter estimator is updated to become,

$$\hat{\theta} = (Z^T Z + \lambda R_0)^{-1} Z^T y. \hfill (21)$$

The $q^{th}$ block entry of the roughness penalties is a matrix of dimensions $n_{\beta,q} \times n_{\beta,q}$ representing the penalisation of the $q^{th}$ term in the functional linear model,

$$R_{0\beta,q} = \int_0^T \left[ D^{(2)}[b_q(t)] \right] \left[ D^{(2)}[b_q(t)^T] \right] dt, \hfill (22)$$

where $b_q(t)^T = [b_{q1}(t), \ldots, b_{q,n_{\beta,q}}(t)]$ are known basis functions for the functional parameters and $D^{(2)}(\cdot)$ is the second derivative. Scalar parameters including the constant parameter for the intercept, are not penalised. i.e., their roughness penalties are zero.

Decisions that need to be made include: the choice of the objective function, the choice of bases systems for the profile factors and the functional parameters and their equivalent number of basis functions, and the choice of smoothing smoothing penalty $\lambda$. Focus is given on the A- and D- optimality objective functions which are the trace and determinant of the variance-covariance matrix of the parameter estimator respectively; see Atkinson, Donev, and Tobias (2007, Chapters 6, 9, and 10),

$$\Psi_A(\Gamma) = \text{tr}[(Z^T Z)^{-1}] \hfill (23)$$

$$\Psi_D(\Gamma) = \det[(Z^T Z)^{-1/p}]$$

$$= \exp\left\{-\frac{1}{p} \log \left[ \det((Z^T Z)) \right] \right\}, \hfill (24)$$

with the coefficient matrix $\Gamma$ from the basis expansion of the profile factors assigned to each run of the experiment being the design matrix, and $p = \sum_{q=1}^{Q} n_{\beta,q}$ the total number of basis functions of the functional parameters, i.e., the total number of columns of the model matrix $Z$. A design $\Gamma^* \in \mathcal{X}$ where $\mathcal{X}$ is the design space, is A- and D- optimal if it minimises $\Psi_A(\Gamma)$ and $\Psi_D(\Gamma)$, respectively.
The objective functions in equations (23) and (24) depend on the model matrix $Z$ which is partitioned in $Q$ column blocks. The solution of the integrals, and hence of $Z$, depend on the basis of the profile factors, the basis of the functional parameters and the coefficient matrices from the basis expansions of the profile factors. Since the basis as well as the number of basis functions of the profile factors and the functional parameters are subject of choice, the missing components in $Z$ are the coefficients. Hence, the design of experiments problem is reduced to the optimisation of the coefficient matrices from the expansion of the profile factors.

3.2 Bayesian approach

In this section a Bayesian approach is followed. As for the traditional linear regression problem, the likelihood function is normally distributed and the prior choice assigned to the unknown parameters $\theta$ and $\sigma^2$ is the of conjugate choice of the normal inverse gamma,

$$\pi(y|\theta, \sigma^2) \sim N(Z\theta, \sigma^2 I_n)$$

$$\pi(\theta, \sigma^2) \sim NIG(\mu, V, a/2, b/2),$$

with $\mu$ the $\sum_{q=1}^{Q} n_{\beta,q}$ prior mean vector of $\theta$, $V$ a known and symmetric $\sum_{q=1}^{Q} n_{\beta,q} \times \sum_{q=1}^{Q} n_{\beta,q}$ matrix, and $a, b$ hyperparameters. Using the Bayes' theorem, the joint prior density and the likelihood function are combined, resulting in the joint posterior density of the functional linear model which is the normal inverse gamma distribution,

$$\pi(\theta, \sigma^2|y) \sim NIG(\theta_N, V_N, a^*/2, b^*/2)$$

(26)

with,

$$V_N = (Z^T Z + V^{-1})^{-1}$$

$$\theta_N = V_N (V^{-1} \mu + Z^T y)$$

$$a^* = a + n$$

$$b^* = b + (\mu^T V^{-1} \mu + y^T y - \theta_N^T V_N^{-1} \theta_N).$$

(27)

In the Bayesian framework, the experimental aim is represented through a utility function. A utility function defines the gain of the experimenter from using the design $\Gamma$, to obtain responses $y$, assuming values for the parameters $\theta$. Thus, a Bayesian optimal design is a design $\Gamma^* \in \mathcal{X}$, that is maximising the expected utility with respect to the joint distribution of the unknown responses and unknown parameters; see Chaloner and Verdinelli (1995),

$$\Psi(\Gamma) = \mathbb{E}_{\theta,y}[u(\theta, y, \Gamma)]$$

$$= \int_{\theta} \int_{y} u(\theta, y, \Gamma) \pi(y|\theta, \Gamma) \pi(\theta) \ dy \ d\theta.$$  

(28)

Common utility functions used in the Bayesian framework for optimal experimental designs are the Negative Squared Error Loss (NSEL) and the Shannon Information Gain (SIG).

NSEL is a utility function in quadratic form,

$$u(\theta, y, \Gamma) = -[\theta - \mathbb{E}(\theta|y, \Gamma)]^T[\theta - \mathbb{E}(\theta|y, \Gamma)],$$
and optimal designs are the designs that maximise the expected NSEL. Thus, (28) results to the objective function,
\[
\Psi(\Gamma) = \mathbb{E}_{y,\theta,\sigma^2} \left( -[\theta - \mathbb{E}(\theta|y,\Gamma)]^T[\theta - \mathbb{E}(\theta|y,\Gamma)] \right).
\] (29)

A design is Bayesian optimal when it maximises the negative of the trace of the variance covariance matrix of the posterior distribution of the unknown coefficients averaged across the joint distribution of the unknown responses and unknown parameters,
\[
\Psi(\Gamma) = \mathbb{E}_{y,\theta,\sigma^2} \left( -[\theta - \mathbb{E}(\theta|y,\Gamma)]^T[\theta - \mathbb{E}(\theta|y,\Gamma)] \right)
= -\frac{b}{a - 2} \text{tr}\left((Z^T Z + V^{-1})^{-1}\right). \tag{30}
\]

The objective function in (30) is known as Bayesian A-optimality, and from the Bayesian perspective, an A-optimal design for the functional linear model is the one that maximises (30).

SIG is a utility function of the difference between the log posterior and the log prior,
\[
u(\beta, y, X) = \log \pi(\beta|y) - \log \pi(\beta)
= \log \pi(y|\beta) - \log \pi(y),
\]
with any rearrangements resulting from an application of the Bayes’ theorem and with the marginal distributions involved given by,
\[
y \sim \mathcal{t}_{a}(Z\mu, b a(I + ZV Z^T)); \quad y|\theta \sim \mathcal{t}_{a}(Z\theta, b a I).
\]

An optimal design is a design that maximises the expected utility of SIG. Thus, (28) results to the objective function,
\[
\Psi(\Gamma) = \mathbb{E}_{y,\theta}(\log \pi(y|\theta) - \log \pi(y)) \tag{31}
\]

A design is Bayesian optimal when it maximises the determinant of the variance covariance matrix of the posterior distribution of the unknown coefficients averaged across the joint distribution of the unknown responses and unknown parameters,
\[
\Psi(\Gamma) = \mathbb{E}_{y,\theta}(\log \pi(y|\theta) - \log \pi(y))
= C \log |Z^T Z + V^{-1}|. \tag{32}
\]
with $C$ a constant. The objective function in (32) is known as Bayesian D-optimality, and from the Bayesian perspective, a D-optimal design for the functional linear model is the one that maximises (32).

3.3 Connection between the two approaches

A connection between the Bayesian and frequentist approaches exists through the roughness penalty and smoothness parameter. The connection comes from the equations of the parameter estimator under the roughness penalty approach in (21) and the posterior mean in (27). It is clear to notice that the prior precision matrix is defined to be $V^{-1} = \lambda R_0$ when the prior mean is centered around zero. The frequentist approach is identical to choosing $\lambda = 0$ and thus, matrix $R_p$ corresponds to the roughness matrix and the smoothing value $\lambda$ controls the wiggliness of a function. Meaning that, a value of $\lambda$ being zero, corresponds to uncertain prior choice and no smoothness, but a value of $\lambda$ tending towards infinity corresponds to a strong prior choice and heavily penalised functions.
4 Step functions illustrative example for a single profile factor

The aim in this example is to identify A-optimal designs and to perform a sensitivity study to investigate how the optimal designs are affected to changes on the settings of the experiment. The functional linear model considered involves the intercept and the main effect of one profile factor. Thus, the functional of the profile factors from (7) is defined as

\[ f_T(x_i(t)) = 1 x_{i1}(t) \]

with \( x_{i1}(t) \) the profile factor at the \( i^{th} \) run of the experiment. For a single profile factor, the functional linear model from equation (9) is simplified to the functional linear model of the form,

\[ y_i = \beta_1 + Z^T \beta_2(t) x_{i1}(t) dt + \epsilon_i, \]

\[ i = 1, 2, \ldots, n, \ t \in [0, 1], \ -1 \leq x_{i1}(t) \leq 1. \]  

(33)

It is assumed that control of the profile factor is represented via a degree zero B-spline, which is equivalent to the step function basis. The design problem is reduced to the optimisation of the \( n \times n_{x,1} \) coefficient matrix \( \Gamma_1 \). Throughout this section, the degree of the B-spline basis is kept fixed. Thus, the complexity of the functions depend only on the choice of knots and the choice of basis for the functional parameter. Knots are assumed to be equally spaced over the time interval \([0, 1]\).

For the functional parameters, linear and quadratic bases are used. The linear and quadratic bases expansions for the functional parameter in (33) are given by,

\[ \beta_2(t) = \theta_{21} + \theta_{22} t, \]

\[ \beta_2(t) = \theta_{21} + \theta_{22} t + \theta_{23} t^2, \]  

(34)

respectively. For the linear basis, there are 2 bases functions, i.e., \( n_{\beta,2} = 2 \), the basis function vector is \( b_2(t) = (1 \ t) \), and the vector of unknown coefficients is \( \theta_2 = (\theta_{21} \ \theta_{22})^T \). For the quadratic basis, there are 3 bases functions, i.e., \( n_{\beta,2} = 3 \), the basis function vector is \( b_2(t) = (1 \ t \ t^2) \), and the vector of unknown coefficients is \( \theta_2 = (\theta_{21} \ \theta_{22} \ \theta_{23})^T \).

The A-optimality objective function in (23) requires that the information matrix to be invertible. Following properties of the rank, the following constraints need to be satisfied: if the basis for the parameters is linear, it is required that \( n_{x,1} \geq 2 \), and if the basis is quadratic, it is required that \( n_{x,1} \geq 3 \). For instance, if the basis for the parameters is linear and \( n_{x,1} = 1 \), there are no interior knots, i.e., only boundary knots. This causes linear dependency in the \( Z^T Z \), thus, non-invertibility. Similarly, \( Z^T Z \) is non-invertible for a quadratic basis for the functional parameter and \( n_{x,1} = 1 \) or 2.

4.1 A-optimal designs using the frequentist approach

To begin with, optimal designs are identified using the frequentist approach. The number of runs considered is \( n \in \{4, 8, 12\} \). Moreover, the number of basis functions considered is \( n_{x,1} \in \{2, 3, 4, 8, 16, 100\} \). Knots are equally spaced. For each experiment the coordinate exchange algorithm (Overstall and Woods, 2017) is used to find A-optimal designs for 1000 random starts (Goos and Jones, 2011).

The results for the linear basis for the functional parameter are available on Table 1. In general, increasing the number of runs gives identical or similar patterns, in more repetitions. Interestingly, one could notice that regardless the number of runs, the objective value for \( n_{x,1} = 3 \) is higher than for \( n_{x,1} = 2, 4 \). This has to do with the choice of nested models, i.e., the knot vector for a model with...
\( n_{x,1} = 2 \), is nested in the knot vector of a model with \( n_{x,1} = 4 \). The design identified for \( n_{x,1} = 3 \) is sub-optimal, and it is the only model that does not include \( t = 0.5 \) in the knot vector. As the number of basis function increases, the designs perform better with respect to A-optimality. However, the drop in the objective values of the optimal designs as \( n_{x,1} \) increases becomes insignificant. This is an indication that a large number of basis functions for the profile factor is not needed.

Table 1: A-optimality values and A-efficiency values with \( n \in \{4, 8, 12\} \) for the linear basis for \( \beta_2(t) \) and step function basis for \( x_1(t) \).

| \( n_{x,1} \) | \( n = 4 \) | \( n = 8 \) | \( n = 12 \) |
|-------|--------|--------|--------|
|       | A-opt  | A-eff  | A-opt  | A-eff  | A-opt  | A-eff  |
| 2     | 8.750  | 0.961  | 3.958  | 0.981  | 2.583  | 0.972  |
| 3     | 8.828  | 0.952  | 4.287  | 0.906  | 2.778  | 0.904  |
| 4     | 8.750  | 0.961  | 3.903  | 0.995  | 2.570  | 0.977  |
| 8     | 8.493  | 0.990  | 3.902  | 0.995  | 2.539  | 0.989  |
| 16    | 8.427  | 0.997  | 3.887  | 0.999  | 2.520  | 0.997  |
| 100   | 8.404  | 1.000  | 3.882  | 1.000  | 2.512  | 1.000  |

The optimal designs achieve at most two changes in the step function. However, most of the designs achieve a single change from -1 to 1 and vice-versa, or no change, i.e., constant function in -1 or 1; see Figure 1 and Figure 2.

The results for the quadratic basis for the functional parameter are available on Table 2. Increasing the number of basis functions causes a more significant change in the objective value compared to the linear basis function. Thus, it makes sense to use more basis functions for the quadratic basis. Having said that, a large number of basis functions is still not needed. The step functions achieve at most three changes, but most of the functions achieve two changes or even a single change. Meaning that, most of the functions found move from -1 to 1 and then back to -1 or the other way round. Three changes in the step function occur mostly for large values of \( n_{x,1} \).

4.2 A-optimal designs using the Bayesian approach

The prior choice for variance is an inverse gamma distribution such that, \( \sigma^2 \sim IG(2,1) \). The basis choice for the functional parameter is the quadratic basis for which \( D^2b_2(t) = (0,0,2) \) and matrix \( R_p \) has a non zero entry, i.e., \( r_{33} = 4 \). The linear basis is not considered because all elements in the roughness penalty matrix are zero. The choice of smoothing values considered are \( \lambda \in \{0.01, 1, 10\} \) and the number of basis functions for the profile factor are \( n_{x,1} \in \{3, 4, 8\} \). The choice of runs for the experiment are \( n \in \{4, 12\} \). The objective values for the Bayesian A-optimal designs are shown in Table 3.

As \( \lambda \) increases, the designs are less complicated, i.e., less changes in the step functions. For Bayesian A-optimal designs and small values of \( \lambda \), there are at most two changes in the step functions. Moreover, for small values of \( \lambda \), the A-optimal designs are similar to the A-optimal designs in the frequentist approach; see Figure 3. However, when \( \lambda \) increases, there is at most one change
Figure 1: Four run A-optimal design for $n_{x,1} = 4$, linear basis for $\beta_2(t)$ and step function basis for $x_{1}(t)$.
Figure 2: Four run A-optimal design for $n_{x,1} = 8$, linear basis for $\beta_2(t)$ and step function basis for $x_1(t)$. 
Table 2: A-optimality values and A-efficiency values with \( n \in \{4, 8, 12\} \) for the quadratic basis for \( \beta_2(t) \) and step function basis for \( x_{1i}(t) \).

| \( n_{x,1} \) | \( n = 4 \) | \( n = 8 \) | \( n = 12 \) |
| | A-opt | A-eff | A-opt | A-eff | A-opt | A-eff |
|---|---|---|---|---|---|---|
| 3 | 386.408 | 0.535 | 189.766 | 0.510 | 126.409 | 0.499 |
| 4 | 246.869 | 0.838 | 103.553 | 0.934 | 67.735 | 0.931 |
| 8 | 218.479 | 0.947 | 99.109 | 0.976 | 65.217 | 0.966 |
| 16 | 208.843 | 0.991 | 97.408 | 0.993 | 63.610 | 0.991 |
| 100 | 206.884 | 1.000 | 96.709 | 1.000 | 63.028 | 1.000 |

Table 3: A-optimality values under the Bayesian approach for \( n \in \{4, 12\} \) and \( \lambda \in \{0.01, 1, 10\} \), for the quadratic basis of \( \beta_2(t) \) for the functional linear model.

| \( \lambda = 0.01 \) | \( \lambda = 1 \) | \( \lambda = 10 \) |
|---|---|---|
| \( n_{x,1} \) | \( n = 4 \) | \( n = 12 \) | \( n = 4 \) | \( n = 12 \) | \( n = 4 \) | \( n = 12 \) |
| 3 | 58.183 | 39.846 | 9.343 | 3.298 | 8.880 | 2.830 |
| 4 | 57.772 | 36.233 | 9.257 | 3.083 | 8.801 | 2.622 |
| 8 | 55.827 | 34.933 | 9.002 | 3.054 | 8.544 | 2.591 |

in the step functions, and the A-optimal designs are similar to the A-optimal designs for the linear basis in the frequentist approach; see Figure 4. This is because, big values of \( \lambda \) penalise wiggly functions and the only term to be penalised is the quadratic term.

## 5 Application to a dynamic experiment in the Ambr250 bioreactor

The Ambr250 bioreactor experiment performed is based on an A-optimal design found using the frequentist approach. The experiment consisted of four factors, three scalar factors, i.e., pH, temperature, IVCC, and one profile factor, i.e., feed volume. The optimal design we proposed is a 12-run design to estimate linear and quadratic effects for the scalar factors, and a quadratic function for the profile factor. The response is the titre content at the final day of the experiment. Thus, the model for the Ambr250 experiment is an extension to the previous model to include three scalar factors in addition to the profile factor,

\[
titre_i = \beta_1 + \int_0^T \beta_2(t) \text{FeedVolume}_{i1}(t) \, dt + \beta_3 \text{pH} + \beta_4 \text{Temperature} + \beta_5 \text{IVCC} + \beta_6 \text{pH}^2 + \beta_7 \text{Temperature}^2 + \beta_8 \text{IVCC}^2 + \epsilon_i, \quad i = 1, \ldots, 12.
\]
Figure 3: Four run Bayesian A-optimal design for $n_{x,1} = 4$, $\lambda = 0.01$, quadratic basis for $\beta_2(t)$ and step function basis for $x_1(t)$. 
Figure 4: Four run Bayesian A-optimal design for $n_{x,1} = 4$, $\lambda = 10$, quadratic basis for $\beta_2(t)$ and step function basis for $x_{1}(t)$. 
Feed volume is dynamically varied over time as a step function, so the control of the profile factor is represented via a degree zero B-spline. The number of basis functions for the profile factor is $n_{x,1} = 4$ resulting from the choice of three equally spaced knots. The A-optimal design proposed has five unique feed volume functions; see Figure 5, with function (a) repeated four times, function (b) repeated five times, and functions (c), (d), and (e) once. The completed runs are defined as combinations of the feed volume function and the values of pH, IVCC, and temperature, as defined in Table 4. The optimal design for the scalar factors includes boundary points and centre points in order to be able to estimate the curvature. This is similar to the behaviour of the quadratic function for the profile factor, where the functions of the profile factor change at most twice.

The fifth run of the design proposed failed to run. For this reason the linear and quadratic effects for the scalar factors and the quadratic function for the profile factor are estimated based on the remaining 11-run design. The title content value at the final day of the experiment is normalised in the range $[0,1]$. For this reason the data are analysed using the logit-transformation.

The response data from the bioreactor are available in 3 decimal places except a single response observation from the 11th run which is 1 and thus, cannot be logit-transformed. However, the response observation of 1 is not exactly equal to 1, but instead lies in the interval $[0.9995, 1]$, which is rounded to 1 in 3 decimal places. On the logit scale the latter titre content interval is $[7.6004, \infty]$. Essentially, that response observation is a censored observation because we have
Table 4: A-optimal design for the Ambr250 bioreactor experiment. The feed volume functions labelled (a)-(d) are demonstrated in Figure 5.

| i | Feed volume | pH  | Temperature | IVCC |
|---|-------------|-----|-------------|------|
| 1 | (a)         | -1  | 1           | 0    |
| 2 | (a)         | 1   | 1           | 1    |
| 3 | (b)         | 1   | -1          | 0    |
| 4 | (c)         | 0   | 0           | 0    |
| 5 | (d)         | 0   | 0           | 0    |
| 6 | (a)         | 1   | 0           | -1   |
| 7 | (e)         | 0   | 0           | 0    |
| 8 | (b)         | -1  | 0           | 1    |
| 9 | (b)         | 0   | 1           | -1   |
|10 | (a)         | 0   | -1          | 1    |
|11 | (b)         | 1   | 0           | 1    |
|12 | (b)         | 0   | 1           | 0    |

some, but not the exact, information, i.e., an interval for the titre content, but not the exact titre content. For this reason, the model choice is a parametric survival model and the contribution of the response observation at 1 is replaced by the survival function \(S(y)\) \((S(y) = 1 - F(y))\) with \(F()\) the distribution function evaluated at 7.6004.

The model selection process to identify the factors that have a significant effect on the titre content was performed via backward selection using the AIC. The main and quadratic effects of the temperature, the pH, and the IVCC have a significant impact on the titre content; see (36) for the point estimates, but on the other hand, the profile factor feed volume does not significantly affect the response,

\[
titre = 1.199 + 1.324 \text{pH} + 1.684 \text{IVCC} \\
+ 0.506 \text{Temperature} - 1.851 \text{Temperature}^2. \tag{36}
\]

In that case, 1.324 and 1.684 represent the estimated positive change in the titre content for a unit change in pH and IVCC, respectively, while \((0.506 - 3.702 \text{Temperature})\) represent the change in the titre content for a unit change in temperature.

6 Discussion

In this paper, a new methodology for finding optimal designs for experiments involving functions of profile factors depending on a scalar response has been demonstrated. The methodology uses
basis function expansions of the profile factors and the functional parameters in a scalar-on-function linear model. It is flexible and can be applied assuming a variety of different bases for both profile factors and parameter functions. For simple functional parameters, e.g. linear, only simple forms for the profile factor are required.

Ongoing work is divided in three parts. The first part is extending the results to "scaled" optimality criteria that are tailored to estimation of the functional parameters. The second part is to extend the current methodology to other than normally distributed responses and finding designs for scalar-on-function generalised linear models. The third part is to develop methods for choosing optimal functions for inputs into the much more challenging dynamic models depending on systems of differential equations.

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