Optimal Design for Estimating the Mean Ability over Time in Repeated Item Response Testing

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Abstract

We present general results on D-optimal designs for estimating the mean response in repeated measures growth curve models with metric outcomes. For this situation, we derive a novel equivalence theorem for checking design optimality. The motivation of this work originates from designing a study in psychological item response testing with multiple retests to measure the improvement in ability. Besides introductory linear growth curves for which analytical results can be obtained, we consider two non-linear growth curve models incorporating an increasing mean ability and a saturation effect. For these models, D-optimal designs are determined by computational methods and are validated by means of the equivalence theorem.

Keyword: D-optimal design; growth curve; repeated measures model; mixed effect model

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1 Introduction

This article is motivated by planning experiments for analyzing retest effects of cognitive abilities. These effects are an important issue in educational sciences since a long time. They refer to score gains through repeated applications of cognitive ability tests, e.g., the Scholastic Aptitude Test. Due to retesting a considerable increase in test performance may arise which has necessarily to be considered to adequately interpret the test results. Very often, retesting of intelligence tests has been studied. According to the results of a recent meta-analysis by Scharfen, Peters and Holling (2018) retesting of general intelligence leads to significant score gains proceeding nonlinearly over the first three test administrations and then reaching a plateau. Furthermore, a relatively large standard deviation of the true effects was observed, meaning that the mean increase of the score gains considerably differs between subjects. Such score gains are usually analyzed by latent growth models representing a class of statistical methods to estimate growth or changes over a period of time. These statistical techniques are widely used in psychology and in other behavioral as well as social sciences. Usually, the longitudinal data to be analyzed are based on the same subjects measured at different time points by the
same tests or by parallel test versions. The growth curves, also called latent trajectories, might take on different forms, e.g., they may be systematically increasing or decreasing over time. Often, a mean trajectory will be estimated as well as individual deviations from this trajectory. The purpose of the present work is to investigate optimal designs for estimating the model parameters for the mean score. We first give a general model description for the response in Section 2. There a key component of the model is that all subjects are observed repeatedly. This leads to models with correlated observations within subjects. For the within subject covariance we will consider two different covariance structures: compound symmetry and autoregressive. In the model assumption a further important feature is that only the number of time points taken is important and that the actual time elapsed between different testings does not play a role. In Section 3 we derive the covariance matrices for the maximum likelihood estimates of the mean score. First, we consider an unstructured behavior of the mean score described by an analysis of variance type model which treats the time points as levels of a single factor. Then, we introduce a straight line model for the mean response curve and two nonlinear models which capture the saturation property of a plateau: a sigmoid (logistic type) and an exponential decay model. These latter models are common candidates in modeling dose response relationships (see e.g. Brenson, Pinheiro and Bretz 2003 or Dette, Bretz, Pepelyshev and Pinheiro 2008). Here, we also derive a general form of the information matrix which relies only on the frequencies of observations at each time point. These frequencies completely determine the properties of a design in the present situation. The quality of a design is measured in terms of the Fisher information matrix since the (asymptotic) covariance matrix of the estimates is proportional to the inverse Fisher information. In Section 4 we summarize some basic facts of the theory of optimal design and obtain analytical results in the case of unstructured and linear mean response curves. We also establish there an equivalence theorem which provides a tool for checking the optimality of a candidate design. For nonlinear models of the mean response curve, the information matrix may depend on the model parameters (see e.g. Silvey 1980, Chapter 6). In that case, we restrict ourselves to locally optimal designs which may depend on nominal values for the parameters (Chernoff 1953). In Section 5 we present numerical results of optimal designs for nonlinear mean response curves when analytical solutions are not available. The article concludes with a short discussion in Section 6. Technical proofs are deferred to the Appendix.

2 General Model Specifications

As outlined in the introduction, the model has to describe the situation where \( N \) subjects are tested at \( J \) time points \( t_1 < \ldots < t_J \) each. The test administered at the \( j \)th time point \( t_j \) consists of the same number \( I_j \) of items for each subject. The total number of items per subject over all time points will be denoted by \( I = \sum_{j=1}^{J} I_j \). The corresponding observation of the score \( y_{nji} \) of subject \( n \) for the \( i \)th item at time point \( t_j \) is modeled as the realization of a random variable \( Y_{nji} \). For each subject the mean of \( Y_{nji} \) is given by the individual ability \( \mu_{nj} \) at time point \( t_j \).

Moreover, as we are interested in a general description of the development of ability over time, we assume that at each time point \( t_j \) the individual abilities \( \mu_{nj} \) deviate randomly from an aggregate population ability \( \mu_j \) at time point \( t_j \).

As a general framework, we assume, that for all time points \( t_j \) the population ability \( \mu_j \) is a function of a \( p \)-dimensional vector \( \beta = (\beta_0 \cdots \beta_{p-1})^T \) of parameters, i.e. \( \mu_j = \mu_j(\beta) \) and \( p \leq J \). The corresponding vector containing the population abilities for all time points is denoted by \( \mu(\beta) = (\mu_1(\beta) \cdots \mu_J(\beta))^T \). Specifically, in Section 3 we will start with considering an unstructured model in which the population ability \( \mu = \beta \) may vary arbitrarily...
over time without any restrictions, i.e. \( p = J \), and then extend the results to structured models in Subsection 3.2 where the population ability depends on time by a functional, potentially nonlinear relationship \((p < J)\).

While observations can be assumed to be uncorrelated between subjects, they will, typically, be correlated within subjects. For modelling this dependence, we introduce the individual abilities \( \mu_{nj} \) as random effects \( \mu_{nj} = \mu_j + \gamma_{nj} \), where \( \gamma_{nj} \) are the individual deviations from the population mean \( \mu_j \) for subject \( n \) at time point \( t_j \). To become more specific, we suppose that the conditional mean of the score \( Y_{nji} \) given the random effect can be described as the difference of the ability \( \mu_{nj} \) of subject \( n \) at time point \( t_j \) and the difficulty \( \zeta_{ji} \) of the item presented, i.e. \( E(Y_{nji} | \gamma_{nj}) = \mu_{nj} - \zeta_{ji} = \mu_j + \gamma_{nj} - \zeta_{ji} \).

The difficulties \( \zeta_{ji} \) of the items presented to the subjects are supposed to be known from previous calibration experiments. As the item difficulties are modeled as additive constants, we may transform the scores to their normalized version \( \tilde{Y}_{nji} = Y_{nji} - \zeta_{ji} \). We, thus, may assume without loss of generality that throughout the remainder of the paper all difficulties are formally set to 0 and, hence, \( E(Y_{nji} | \gamma_{nj}) = \mu_{nj} = \mu_j + \gamma_{nj} \). As a consequence, only the numbers \( I_j \) of items at each time point \( t_j \) are relevant for design considerations.

In the present situation, the individual observations are modeled by the linear mixed model

\[
Y_{nji} = \mu_j + \gamma_{nj} + \varepsilon_{nji},
\]

\( i = 1, \ldots, I_j, \ j = 1, \ldots, J, \ n = 1, \ldots, N \). The errors \( \varepsilon_{nji} \) are assumed to be uncorrelated and normally distributed with zero mean and variance \( \sigma^2 \).

Also the random effects \( \gamma_{nj} \) are assumed to be jointly normally distributed with zero mean, and to be independent between subjects, i.e. \( \text{cov}(\gamma_{nj}, \gamma_{n'j'}) = 0 \) for \( n \neq n', j, j' = 1, \ldots, J \), but that there is a within subject covariance \( \sigma^2_{jj'} \), i.e. \( \text{cov}(\gamma_{nj}, \gamma_{n'j'}) = \sigma_{jj'}, \ j \neq j', n = 1, \ldots, N \). Also assume, that the errors and random effects are uncorrelated, i.e. \( \text{cov}(\varepsilon_{nji}, \gamma_{n'j'}) = 0 \), for all \( i = 1, \ldots, I_j, j, j' = 1, \ldots, J, \) and \( n, n' = 1, \ldots, N \). Denote the vector of individual deviations for subject \( n \) by \( \gamma_n = (\gamma_{n1} \cdots \gamma_{nj})^T \). For these random effects, we assume that they are independent identically multivariate normal with zero mean and nonnegative definite covariance matrix \( \Sigma_{\gamma} \), with entries \( \sigma_{jj'} \).

For the within subject covariance structure we deal with two different models which are commonly used to describe the within subject dependence: Compound symmetry and an autoregressive (AR(1)) correlation structure.

In the case of compound symmetry, it is assumed that the correlation between all repetitions is the same for all pairs of distinct time points. Then the covariance matrix is given by \( \Sigma_{\gamma, CS} = \sigma_{\gamma}^2 \begin{pmatrix} \sigma^2_{11} & \sigma^2_{12} & \cdots & \sigma^2_{1J} \\ \sigma^2_{21} & \sigma^2_{22} & \cdots & \sigma^2_{2J} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma^2_{J1} & \sigma^2_{J2} & \cdots & \sigma^2_{JJ} \end{pmatrix} \), where \( \sigma_{\gamma}^2 > 0 \) is the variance of the random effects \( \gamma_{nj} \), \( \rho \) is the correlation of the random effects within subjects, \( \mathbf{I}_m \) is the \( m \times m \) identity matrix, and \( \mathbf{1}^T_m = (1 \cdots 1)^T \) denotes the \( m \)-dimensional vector with all entries equal to 1. We additionally assume that the within subject correlation is nonnegative, \( 0 \leq \rho \leq 1 \). Note that compound symmetry occurs when the random effects split up additively \((\gamma_{nj} = \tilde{\gamma}_{n0} + \tilde{\gamma}_{nj})\) into a common block effect \( \tilde{\gamma}_{n0} \) with variance \( \rho^2 \) which is constant over time and independent identically distributed time effects \( \tilde{\gamma}_{nj} \) with variance \( (1 - \rho)^2 \). In the autoregressive covariance structure the correlation between neighboring time points is higher than the correlation of those, which are farther away. More specifically, for AR(1), we have \( \sigma_{jj'} = \sigma^2_{\gamma} \rho^{|j-j'|} \), i.e.

\[
\Sigma_{\gamma, AR} = \sigma_{\gamma}^2 \begin{pmatrix} 1 & \rho & \rho^2 & \cdots & \rho^{J-1} \\ \rho & 1 & \rho & \cdots & \rho^{J-2} \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ \rho^{J-2} & \cdots & \rho & 1 & \rho \end{pmatrix}.
\]
with $\sigma_\gamma^2 > 0$. Also here we additionally assume that the within subject correlation is nonnegative, $0 \leq \rho \leq 1$.

To display distributional properties of the model and to derive expressions for parameter estimates, it is convenient to rewrite the model in vector notation. The vectors of observations and errors for subject $n$ at time point $t_j$ are $\mathbf{Y}_{nj} = (Y_{nj1}, \ldots, Y_{njt_j})^T$ and $\mathbf{e}_{nj} = (\varepsilon_{nj1}, \ldots, \varepsilon_{njt_j})^T$, respectively.

The vector $\mathbf{Y}_{nj}$ of observations for subject $n$ at time point $t_j$ is modeled by

$$\mathbf{Y}_{nj} = 1_{I_j} \mu_j + 1_{I_j} \gamma_{nj} + \mathbf{e}_{nj},$$

where $j = 1, \ldots, J$, $n = 1, \ldots, N$. Then $\mathbf{Y}_{nj}$ is $I_j$-dimensional multivariate normal with expectation $\mathbb{E}(\mathbf{Y}_{nj}) = 1_{I_j} \mu_j$ and covariance matrix $\text{Cov}(\mathbf{Y}_{nj}) = \sigma_\varepsilon^2 1_{I_j} + \sigma_{\gamma j} 1_{I_j} 1_{I_j}^T$. Moreover, within subjects observational vectors have covariance $\text{Cov}(\mathbf{Y}_{nj}, \mathbf{Y}_{nj'}) = \sigma_{\gamma jj'} 1_{I_j} 1_{I_j'}^T$, $j,j' = 1, \ldots, J$, $j \neq j'$, $n = 1, \ldots, N$, and observational vectors are uncorrelated between subjects, $\text{Cov}(\mathbf{Y}_{nj}, \mathbf{Y}_{n'j'}) = 0$ for $n \neq n'$, where $0$ is a generic zero matrix of appropriate size.

Denote by $\mathbf{F}_n = \text{diag}_{j=1,\ldots,J}(1_{I_j})$ the individual design matrix for subject $n$, where diag$_{j=1,\ldots,J}(\mathbf{C}_j)$ denotes a $\sum_{j=1}^J m_j \times \sum_{j=1}^J n_j$ block diagonal matrix with diagonal blocks $\mathbf{C}_j$ of size $m_j \times n_j$ and off-diagonal zero matrices $0$ of appropriate size. Remember that all individuals receive the same design, i.e., $\mathbf{F}_n = \mathbf{F}$, say, for all $n = 1, \ldots, N$. Then the model for all observations $\mathbf{Y}_n = (\mathbf{Y}_n^T_1, \ldots, \mathbf{Y}_n^T_N)^T$ of a subject $n$ can be written in vector notation as

$$\mathbf{Y}_n = \mathbf{F} \mu + \mathbf{F} \gamma_n + \mathbf{e}_n,$$

where $\mathbf{e}_n = (\mathbf{e}^T_{n,1}, \ldots, \mathbf{e}^T_{n,J})^T$ is the corresponding error vector for subject $n$. Then for each subject the observation vector $\mathbf{Y}_n$ is $I$-dimensional multivariate normal with expectation $\mathbb{E}(\mathbf{Y}_n) = \mathbf{F} \mu$ and covariance matrix $\mathbf{V}_n = \text{Cov}(\mathbf{Y}_n) = \sigma_\varepsilon^2 \mathbf{I}_I + \mathbf{F} \Sigma_\gamma \mathbf{F}^T$.

Note that also the individual covariances are identical, $\mathbf{V}_n = \mathbf{V}$, for all individuals $n = 1, \ldots, N$. Further, because at each time point $t_j$ all subjects have to respond to the same number $I_j$ of items, the model equation of the vector $\mathbf{Y} = (\mathbf{Y}_1^T, \ldots, \mathbf{Y}_N^T)^T$ of all observations has a product-type structure

$$\mathbf{Y} = (\mathbf{1}_N \otimes \mathbf{F}) \mu + (\mathbf{1}_N \otimes \mathbf{F}) \gamma + \mathbf{e},$$

where $\gamma = (\gamma_1^T, \ldots, \gamma_N^T)^T$ is the $NJ$-dimensional stacked vector of all random effects, $\mathbf{e} = (\mathbf{e}_1^T, \ldots, \mathbf{e}_N^T)^T$ is the $NI$-dimensional stacked vector of error terms, and “$\otimes$” denotes the Kronecker product of matrices and vectors, respectively.

Observations from different subjects $n$ and $n'$ are uncorrelated, $\text{Cov}(\mathbf{Y}_n, \mathbf{Y}_{n'}) = 0$. The vector of the random components and the vector of the error terms are multivariate normal with zero mean and covariance matrix $\text{Cov}(\gamma) = \mathbf{I}_N \otimes \Sigma_\gamma$ and $\text{Cov}(\mathbf{e}) = \sigma_\varepsilon^2 \mathbf{I}_N I$, respectively. As a consequence, $\mathbf{Y}$ is multivariate normal with expectation $\mathbb{E}(\mathbf{Y}) = (\mathbf{1}_N \otimes \mathbf{F}) \mu$ and covariance matrix $\text{Cov}(\mathbf{Y}) = \mathbf{I}_N \otimes \mathbf{V}$. Note, that the individual covariance matrix $\mathbf{V}$ and, hence, $\text{Cov}(\mathbf{Y})$ is non-singular, since $\mathbf{V} \succeq \sigma_\varepsilon^2 \mathbf{I}_I > 0$, where, for matrices, the relations “$\succeq$” and “$>$” are meant in the sense of nonnegative and positive definiteness, respectively.

### 3 Mean Response Curves

To derive results for the situation that the mean responses $\mu_1, \ldots, \mu_J$ are emerging from a growth curve with only few parameters, we first start with an unstructured case in which the time points $t_1, \ldots, t_J$ may be considered as levels in a one-way layout model.
3.1 Analysis of Variance Type Model (Unstructured Time Dependence)

We start with assuming $\mu = \beta$ without imposing any restrictions on $\mu_j = \beta_j$, $j = 1, \ldots, J$. Hence, the time points may be interpreted as levels of a single factorial variable “time”. Estimation of the mean score in this model results in estimating $\beta = \mu$. Under the normality assumption, the maximum-likelihood estimator is a generalized least squares estimator which is given by

$$\hat{\beta} = \left( (I_N \otimes F)^T (I_N \otimes V)^{-1} (I_N \otimes F) \right)^{-1} (I_N \otimes F)^T (I_N \otimes V)^{-1} Y$$

$$= \frac{1}{N} \sum_{n=1}^{N} (F^T V^{-1} F)^{-1} F^T V^{-1} Y_n = \frac{1}{N} \sum_{n=1}^{N} \hat{\beta}_n,$$  \hspace{1cm} (1)

where $\hat{\beta}_n = (F^T V^{-1} F)^{-1} F^T V^{-1} Y_n$ is the estimated mean score based on a single subject $n$, $n = 1, \ldots, N$ (see e.g. [Rao, 1973], Chapter 4, for the general structure, and [Entholzner et al., 2005] for the representation as an average of individual fits). As the individual covariance matrix $V$ and the individual design matrix $F$ interchange in the sense $VF = FU$, where $U = \Sigma_{\gamma} \text{diag}_{j=1,\ldots,J}(I_j) + \sigma^2_\epsilon I_J$, the individual generalized least squares estimator $\hat{\beta}_n$ and the ordinary least squares estimator $\hat{\beta}_{n,OLS} = (F^T F)^{-1} F^T Y_n$ based on the observations of subject $n$ coincide (see [Zyskind, 1967]). Accordingly, also in the full model, the covariance matrix $I_N \otimes V$ and the design matrix $I_N \otimes F$ interchange, $(I_N \otimes V)(I_N \otimes F) = (I_N \otimes F)U$. Thus, also in the full model, the generalized least squares estimator $\hat{\beta}$ and the ordinary least squares estimator $\hat{\beta}_{OLS} = (\hat{\beta}_1, \ldots, \hat{\beta}_J)^T$ coincide, where $\hat{\beta}_j = \frac{1}{N J} \sum_{n=1}^{N} \sum_{i=1}^{J} Y_{nji}$ is the average score at the $j$th time point over all subjects $n = 1, \ldots, N$. Thus, $\hat{\beta} = \hat{\beta}_{OLS}$ does not depend on the particular form of $V$ and, hence, does not depend on $\Sigma_\gamma$.

The covariance matrix of $\hat{\beta}$ is

$$\text{Cov}(\hat{\beta}) = \frac{1}{N} (F^T V^{-1} F)^{-1}.$$  \hspace{1cm} (2)

For the estimability of $\beta$ observations have to be made at all time points, i.e. $I_j > 0$ for all $j = 1, \ldots, J$. The covariance matrix of $\hat{\beta}$ can be expressed as

$$\text{Cov}(\hat{\beta}) = \frac{1}{N} \left( \sigma^2_\epsilon M_0^{-1} + \Sigma_\gamma \right),$$  \hspace{1cm} (3)

where $M_0 = F^T F = \text{diag}_{j=1,\ldots,J}(I_j)$ is the information matrix in the corresponding linear fixed effects model of a one-way layout with time points $t_j$ as levels. The representation (3) is in accordance with the results given in [Entholzner et al., 2005].

Note that the covariance matrix becomes smaller, in the sense of nonnegative definiteness, if the numbers $I_j$ of items are increased or the number $N$ of subjects becomes larger. However, consistency of the estimator is only achieved if the number $N$ of subjects tends to infinity while increasing the numbers $I_j$ of items will only reduce the covariance matrix to $\frac{1}{N} \Sigma_\gamma$.

In the case of compound symmetry of the within covariance matrix $\Sigma_{\gamma,CS}$ the covariance matrix of $\hat{\beta}$ can be written as

$$\text{Cov}(\hat{\beta}) = \frac{\sigma^2_\gamma}{N} \left( \text{diag}_{j=1,\ldots,J} \left( 1 - \rho + \frac{1}{t_j I_j} \right) + \rho I_J F_J^T \right),$$

where $\tau^2 = \sigma^2_\gamma/\sigma^2_\epsilon$ denotes the variance ratio. If the number of items is equal at each time point, i.e. $I_j = I/J$ for all $j = 1, \ldots, J$, then also the covariance matrix of $\hat{\beta}$ can be seen to be compound symmetric.
In the case of an autoregressive within covariance matrix $\Sigma_{\gamma,AR}$ the covariance matrix of the estimator $\hat{\beta}$ is given by

$$
\text{Cov}(\hat{\beta}) = \frac{\sigma^2}{N} \begin{pmatrix}
\frac{1}{\tau_1} & \rho & \rho^2 & \cdots & \rho^{J-1} \\
\rho & 1 + \frac{1}{\tau_1} & \rho & \cdots & \rho^{J-2} \\
\vdots & \vdots & \ddots & \ddots & \vdots \\
\rho^{J-2} & \cdots & \rho & 1 + \frac{1}{\tau_1} & \rho \\
\rho^{J-1} & \cdots & \rho^2 & \rho & 1 + \frac{1}{\tau_1}
\end{pmatrix}.
$$

### 3.2 Parameterized Growth Curves

In this subsection we treat some commonly used parametric models for the mean scores $\mu_j(\beta)$. For the time points $t_j$ we assume that they are equally spaced, $t_j = j - 1$, because we are not interested in the actual time between tests, but only in the number of tests taken so far.

For illustrative purposes, we start with a simple straight line growth curve. The time trend for the $j$th time point corresponds to the initial value (offset) of the mean response at the beginning of the testing period, $\beta_0$ is determined by

$$
\mu_j(\beta) = \beta_1 - (\beta_1 - \beta_0) \exp(-\beta_2 t_j), \quad j = 1, \ldots, J,
$$

and $\beta = (\beta_0 \quad \beta_1 \quad \beta_2)^T$, $\beta_0 < \beta_1$, $\beta_2 > 0$. In the exponential model the parameter $\beta_0$ corresponds to the initial value (offset) of the mean response at the beginning of the testing period, $t_1 = 0$. The asymptote (saturation level) for $t \to \infty$ is given by $\beta_1$ and the strength of the slope (speed of saturation) is determined by $\beta_2$.

Alternatively, we also consider a sigmoid (four parameter logistic) model given by

$$
\mu_j(\beta) = \beta_0 + \frac{1}{1 + \exp(-(\beta_2 t_j + \beta_3))}, \quad j = 1, \ldots, J,
$$

and $\beta = (\beta_0 \quad \beta_1 \quad \beta_2 \quad \beta_3)^T$, $\beta_0 < \beta_1$, $\beta_2 > 0$. This model is closely related to the Hill equation or the so called $E_{\text{max}}$-model [Reeve and Turner, 2013]. In this model the parameter $\beta_0$ corresponds to the asymptote (baseline) for $t \to -\infty$. Also here $\beta_1$ is the asymptote for $t_j \to \infty$ and $\beta_2$ is the strength of the slope. The last parameter, $\beta_3$, indicates the location of the $ED_{50} = -\beta_3/\beta_2$, where half of the saturation is achieved. In contrast to the four parameter logistic model for binary data, where $\mu_j(\beta)$ is the probability of response at time point $j$, here $\beta_0$ and $\beta_1$ are not restricted to $0 \leq \beta_0 < \beta_1 \leq 1$.

Note, that in the sigmoid model the $ED_{50}$ corresponds to the inflection point of the mean score function. If the $ED_{50}$ is negative, the shape of the sigmoid and the exponential model yield similar results in practical situations. Some examples for the shape of the mean functions for different values of the parameters are shown in Figure [1].

The parameter vector $\beta$ will commonly be estimated by the maximum-likelihood estimator $\hat{\beta}$. To allow for estimability of $\beta$, the number of time points must be at least as large as the number of parameters ($J \geq p$). When the covariance matrix $V$ is known, the log-likelihood for estimating $\beta$ is given by

$$
l(\beta) = -\frac{NJ}{2} \log(2\pi) - \frac{N}{2} \log(\text{det}(V)) - \frac{1}{2} \sum_{n=1}^{N} (Y_n - F\mu(\beta))^T V^{-1} (Y_n - F\mu(\beta)).
$$
The maximum-likelihood estimator $\hat{\beta}$ of $\beta$ is obtained by equating the derivative of the log-likelihood to zero. Only the last expression on the right hand side depends on $\beta$, hence, the derivative of the log-likelihood with respect to $\beta$ is

$$\frac{\partial l(\beta)}{\partial \beta} = \sum_{n=1}^{N} A_{\beta}^{T} F^{T} V^{-1} (Y_{n} - F \mu(\beta)),$$

where

$$A_{\beta} = \begin{pmatrix} \frac{\partial \mu_{1}(\beta)}{\partial \beta_{0}} & \cdots & \frac{\partial \mu_{1}(\beta)}{\partial \beta_{p-1}} \\ \vdots & \ddots & \vdots \\ \frac{\partial \mu_{J}(\beta)}{\partial \beta_{0}} & \cdots & \frac{\partial \mu_{J}(\beta)}{\partial \beta_{p-1}} \end{pmatrix}$$

denotes the Jacobian matrix of $\mu(\beta)$, i.e. the $J \times p$ matrix of the first derivatives with respect to $\beta$.

The quality of the maximum-likelihood estimator is measured by the Fisher information matrix $M_{\beta}$ which is proportional to the inverse of the asymptotic covariance matrix of $\hat{\beta}$, as long as $\beta$ is estimable, i.e. $A_{\beta}$ has full column rank $p$ and is in the span of $F^{T}$. By the definition of the Fisher information for all observations the whole experiment yields

$$M_{\beta} = \text{Cov} \left( \frac{\partial l(\beta)}{\partial \beta} \right) = N A_{\beta}^{T} F^{T} V^{-1} F A_{\beta}.$$ (6)

When the number $I_{j}$ of observations is greater than 0 for each time point $t_{j}$, we can make use of the representation (3) in the unstructured situation of Subsection 3.1. With this representation the information matrix simplifies to

$$M_{\beta} = N A_{\beta}^{T} \left( \sigma_{\epsilon}^{2} M_{0}^{-1} + \Sigma_{\gamma} \right)^{-1} A_{\beta},$$ (7)

where $M_{0} = F^{T} F = \text{diag}_{j=1,...,J}(I_{j})$ denotes the corresponding information matrix in the linear fixed effects model of a one-way layout with time points $t_{j}$ as levels.

In general, when there may be time points $t_{j}$ without observations ($I_{j} = 0$), we can give a more general representation of the core expression $F^{T} V^{-1} F$ in the Fisher information matrix (6).
Lemma 1. Denote by $M_0^{1/2} = \text{diag}_{j=1,\ldots,J}(\sqrt{I_j})$. Then

$$F^T V^{-1} F = M_0^{1/2} \left( \sigma^2 \mathbf{I}_J + M_0^{1/2} \Sigma_0 M_0^{1/2} \right)^{-1} M_0^{1/2}. \quad (8)$$

The proof is given in the Appendix. By Lemma 1 the Fisher information matrix has the form

$$M_\beta = N A_\beta^T M_0^{1/2} \left( \sigma^2 \mathbf{I}_J + M_0^{1/2} \Sigma_0 M_0^{1/2} \right)^{-1} M_0^{1/2} A_\beta. \quad (9)$$

This Fisher information is non-singular if $\beta$ is estimable.

In the particular case of a linearly parameterized mean response, like the straight line growth curve, the Jacobian $A_\beta = A$ does not depend on $\beta$ as $\mu(\beta) = \mathbf{A} \beta$. In this case, for a subject $n$, the mixed effects model can be written as $Y_n = FA_\beta + F \gamma_n + \varepsilon_n$. Then $FA$ is the design matrix of the fixed effects part on the individual level. If $\beta$ is estimable, the maximum-likelihood estimator is unique and coincides with the generalized least squares estimator $\hat{\beta}_{GLS} = \frac{1}{N} \sum_{n=1}^N (A^T F^T V^{-1} F A)^{-1} A^T F^T V^{-1} Y_n$. As in the unstructured situation of the previous subsection, the generalized least square estimator is equal to the estimator $(A^T F^T V^{-1} F A)^{-1} A^T F^T V^{-1} A_\beta$ for an average individual $Y = \frac{1}{N} \sum_{n=1}^N Y_n$ as well as to the average $\frac{1}{N} \sum_{n=1}^N \hat{\beta}_{n, GLS}$ of individual fits $\hat{\beta}_{n, GLS} = (A^T F^T V^{-1} F A)^{-1} A^T F^T V^{-1} Y_n$ based solely on the observations of single subjects $n$. However, in contrast to the unstructured case, the generalized least squares estimator differs in general from the ordinary least squares estimator, which can be seen from the example of the ratio model below.

For the exponential model, the derivatives of $A_\beta$ with respect to the parameters $\beta_0$, $\beta_1$, and $\beta_2$ are

$$\frac{\partial \mu_j(\beta)}{\partial \beta_0} = \exp(-\beta_2 t_j), \quad \frac{\partial \mu_j(\beta)}{\partial \beta_1} = 1 - \frac{\partial \mu_j(\beta)}{\partial \beta_0}, \quad \text{and} \quad \frac{\partial \mu_j(\beta)}{\partial \beta_2} = t_j (\beta_1 - \beta_0) \frac{\partial \mu_j(\beta)}{\partial \beta_0}. \quad (10)$$

The corresponding derivatives for the logistic model are

$$\frac{\partial \mu_j(\beta)}{\partial \beta_0} = \frac{1}{1 + \exp(\beta_2 t_j + \beta_3)}, \quad \frac{\partial \mu_j(\beta)}{\partial \beta_1} = 1 - \frac{\partial \mu_j(\beta)}{\partial \beta_0}, \quad \text{and} \quad \frac{\partial \mu_j(\beta)}{\partial \beta_2} = t_j \frac{\partial \mu_j(\beta)}{\partial \beta_3}, \quad \text{and} \quad \frac{\partial \mu_j(\beta)}{\partial \beta_3} = (\beta_1 - \beta_0) \frac{\exp(\beta_2 t_j + \beta_3)}{(1 + \exp(\beta_2 t_j + \beta_3))^2}. \quad (11)$$

Note that in both of these two model specifications the derivatives depend less on the specific values for $\beta_0$ for the baseline and $\beta_1$ for the saturation level themselves, but on their difference $\beta_1 - \beta_0$. In the particular case of a linear model also the Fisher information $M_\beta = M$ does not depend on the vector $\beta$ of location parameters.

4 Optimal Designs

A design, i.e. a plan how to conduct an experiment, usually has two parts: Firstly we need to know which conditions to observe, which in our case corresponds to the time points $t_j$. The second part of a design determines, how many observations should be spent at each time point. As mentioned at the beginning of the preceding section, the time points $t_j = j - 1$ are fixed, i.e. we need not optimize with respect to the time points. Thus, in the present situation, a design can be described by the numbers $I_j$ of observations at each time point under the constraint that the total number $\sum_{j=1}^J I_j$ of observations equals $I$ and will be denoted by $\xi = (I_1, \cdots, I_J)$. When $I_j \geq 0$ are integers, the design is called an exact design. Actually, we may allow one or more of the numbers $I_j$ to be equal to zero, which means that no observations
are made at the corresponding time points. These kind of designs can be used directly. However, to optimize integers \( I_j \) is a discrete optimization problem which may be hard to solve. If \( I_j \geq 0 \) are relaxed to be real numbers, the design \( \xi \) is called an approximate design (see Kiefer [1959]). The latter is appealing, because it is possible to use methods from convex optimization to optimize with respect to the design. While this yields benchmark designs, rounding of the real numbers \( I_j \) to integers may become necessary for using these designs in applications.

For an approximate design \( \xi \), the standardized (per unit) information matrix \( M_\beta(\xi) = \frac{1}{N} M_\beta \) is defined by the representations (7) and (9), respectively. While for a linear model of the mean score, like the unstructured model of Subsection 3.1 or the straight line growth curve model, the information matrix \( M_\beta(\xi) \) does not depend on the value of the parameter vector \( \beta \), such a dependence will typically occur when the mean score is a nonlinear function over time.

To measure the performance of a design, we will use the \( D \)-criterion which is invariant with respect to reparameterization and scaling and which aims at minimizing the volume of the asymptotic confidence ellipsoid for estimating \( \beta \). Then a design \( \xi^* = (I_{\xi 1} \cdots I_{\xi J}) \) will be called locally \( D \)-optimal for a specific value of \( \beta \) if
\[
\log \det(M_\beta(\xi^*)) \geq \log \det(M_\beta(\xi))
\]
for all \( \xi \) with non-singular information matrix such that \( \beta \) is estimable, i.e. for approximate designs, \( A_\beta \) has full column rank \( p \) and is in the span of the standardized (per unit) information matrix \( M_0(\xi) = \text{diag}_{j=1, \ldots, J}(I_j) \) for \( \xi \) in the corresponding one-way layout model.

Lemma 2. The \( D \)-criterion \( \log \det(M_\beta(\xi)) \) is a continuous, concave function of \( \xi \) on the set of all designs for which \( \beta \) is estimable.

Proof. The continuity can be seen from the general representation of the Fisher information matrix in [9]. For fully supported designs, which take \( I_j > 0 \) observations at each of the \( J \) time points \( j = 1, \ldots, J \), the concavity follows directly from Lemma 2 in Schmelter (2007). The concavity extends to all designs for which \( \beta \) is estimable by the continuity of the criterion. \( \square \)

For a given design \( \xi \), its performance can be compared to the optimal design \( \xi^* \) in terms of the efficiency which is defined by
\[
\left( \frac{\det(M_\beta(\xi))}{\det(M_\beta(\xi^*))} \right)^{1/p}.
\]
Here \( \det(M)^{1/p} \) is the homogeneous version of the \( D \)-criterion such that the efficiency can be interpreted as the proportion of units needed when the optimal design \( \xi^* \) is used to obtain the same precision as for the design \( \xi \) under consideration.

4.1 The Case \( J = p \)
If the number \( J \) of time points is equal to the number \( p \) of parameters, then \( A_\beta \) is a quadratic matrix and consequently
\[
\log \det(M_\beta(\xi)) = -\log \det(\sigma^2_\xi M_0(\xi)^{-1} + \Sigma_\gamma) + c,
\]
where \( c \) denotes a generic constant not depending on \( \xi \). This covers also the situation of unstructured time dependence of Subsection 3.1 when \( A_\beta = I_J \).

Note that, in general, the matrix \( A_\beta \) has to be non-singular in order to allow for estimability of the parameter vector. Since the time points are fixed, the determinant of the Jacobian matrix \( A_\beta \) is constant with respect to the design \( \xi \). Hence, the locally \( D \)-optimal design \( \xi^* \) does not depend on \( \beta \). In particular, the design \( \xi^* \) maximizes \( \log \det(Cov_\xi(\hat{\mu})) \), i.e. it coincides with the \( D \)-optimal design to estimate \( \mu \) in the case of the unstructured model in Subsection 3.1 independent of the parameterization \( \mu = \mu(\beta) \).
In the case of compound symmetry, the covariance matrix $\Sigma_{\gamma,CS}$ is invariant with respect to permutations of the time points. This is also reflected in the criterion in terms of the determinant. For time reversal, the frequencies $I_j$ can be written as $|I_j - I_j'| \leq 1$, $j \neq j'$. More formally, denote by $[a]$ the integer part of $a$ and by $m \mod n = m - n[m/n]$ the remainder of $m$ with respect to division by $n$ for integers $m$ and $n$.

**Lemma 3.** Let $J = p$ and the covariance structure be compound symmetry, then an exact design is D-optimal if $I_j = [I/J] + 1$ for $J' = I \mod J$ time points and $I_j = [I/J]$ for $J - J'$ time points.

In particular, if $I$ is a multiple of $J$, then the uniform design is D-optimal which assigns $I_j = I/J$ items to each of the time points $j = 1, \ldots, J$.

This result can be obtained by standard arguments from the concavity of the D-criterion and the exchangeability of the time points under compound symmetry.

By the strict concavity of the D-criterion, we obtain for the approximate design

**Lemma 4.** Let $J = p$ and the covariance structure be compound symmetry, then

$$\xi^* = \left(\begin{array}{cccc} \frac{1}{J} & \cdots & \frac{1}{J} \end{array}\right)$$

is the D-optimal approximate design.

In the case of autoregressive covariance, there is less symmetry structure available in the covariance matrix $\Sigma_{\gamma,AR}$. Only time reversal does not alter the covariance matrix and, hence, the determinant. For time reversal, the frequencies $I_j$ and $I_{J-j+1}$ have to be interchanged within each symmetric pair of time points $(j, J-j+1)$, $1 \leq j \leq J/2$.

**Lemma 5.** Let $J = p$ and the covariance structure be autoregressive, then the optimal approximate design is symmetric in time, i.e. it is of the form

$$\xi^* = \left(\begin{array}{cccc} I_1^* & I_2^* & \cdots & I_{J/2}^* \end{array}\right)$$

if $J$ is even, and

$$\xi^* = \left(\begin{array}{cccc} I_1^* & I_2^* & \cdots & I_{(J+1)/2}^* \end{array}\right)$$

if $J$ is odd.

Also this result follows by concavity and invariance of the D-criterion.

In the particular case of $J = 3$ time points, under the assumption of an autoregressive correlation structure, the optimal design has the form $\xi^* = (I_1^* I_2^* I_1^*)$, where $I_2^* = I - 2I_1^*$. Hence, optimization has only to be done with respect to the single variable $I_1$. Moreover, in terms of weights $w_j = I_j/I$, the optimal weight $w_1^*$ depends on the sample size $I$ and the variance components $\sigma_2^2$ and $\sigma_3^2$ only through the standardized variance ratio $a = I\tau^2 = I(1 - a^2)/(1 - 3a + a^2) - a^2 \rho^2 w(1 - 2w)^2 + a^2 \rho^4 w^3$ in $0 < w \leq 1/2$. Note that for the uncorrelated case ($\rho = 0$) and for
the case of a constant subject effect ($\rho = 1$) the optimal weight is $w_1^* = 1/3$ in accordance with the situation of compound symmetry. For fixed standardized variance ratios of $a = 50$, $100$ and $200$, the optimal weight $w_1^*$ is shown in Figure 2 in dependence on the correlation $\rho$. From this figure it can be seen that the optimal weight $w_1^*$ is slightly descending in the correlation for small to moderate values of $\rho$ and then ascending back to $1/3$ for large values of the correlation $\rho$. However, the gain of the optimal design is not substantial here as, for $a = 50$, $100$ and $200$, the uniform design ($w = 1/3$) has efficiency of more than $99.5\%$.

4.2 The Case $J > p$

When the number $J$ of time points is larger than the number $p$ of parameters, estimability of the parameter vector $\beta$ requires that $A_\beta$ has full column rank $p$ and that observations are made at, at least, $p$ different time points, i.e. $I_j > 0$ for, at least, $p$ distinct time points $t_j$. In this case, optimal designs may be restricted to a proper subset of time points. However, as we will see, fully supported designs, which take $I_j > 0$ observations at each of the $J$ time points $j = 1, \ldots, J$, will play an important role.

For illustrative purposes we start here with two linear models for the mean response: The straight line growth model and, even simpler, the ratio model.

In the ratio model the mean response is fitted as a straight line $\mu_j(\beta) = \beta_1 t_j$ through the offset $t_1 = 0$. Here $p = 1$, and we consider only $J = 2$ time points $t_1 = 0, t_2 = 1$ such that the correlation structure reduces to $\Sigma_j = \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$ in both the compound symmetry and the autoregressive case. For uncorrelated time points ($\rho = 0$), observations at $t_1 = 0$ do not bear any information on the parameter $\beta = \beta_1$. Then the optimal design $\xi^*$ is minimally supported and assigns all items to the second time point $t_2 = 1$ as in the corresponding fixed effects model without random effects. However, for correlated time points ($\rho > 0$), the situation changes. Observed response at the offset $t_1 = 0$ can be used to better estimate the ratio $\beta_1$ and a fully supported design becomes optimal if the standardized variance ratio $a = I\tau^2 = I\sigma^2_\gamma/\sigma^2_\epsilon$ is sufficiently large: $a > 1/\rho$. Then the optimal design $\xi^*$ assigns only a proportion $I_2^*/I = w^* = (a + 1)/(a + a\rho) < 1$ of items to the effective time point $t_2 = 1$ and
Figure 3: Optimal weight \( w^* = I_2^* / I \) with respect to \( a = I \tau^2 \) for the ratio model \((J = 2, p = 1)\) for different values of \( \rho \) (dashed \( \rho = 0.25 \), solid \( \rho = 0.5 \), dotted \( \rho = 0.8 \), dash-dotted \( \rho = 0.99 \)).

Figure 4: Efficiency of the minimally supported design \((w = 1; \text{left})\) and of the uniform design \((w = 1/2; \text{right})\) with respect to \( a = I \tau^2 \) for the ratio model \((J = 2, p = 1)\) for different values of \( \rho \) (dashed \( \rho = 0.25 \), solid \( \rho = 0.5 \), dotted \( \rho = 0.8 \), dash-dotted \( \rho = 0.99 \)).
the remaining proportion \(1 - w^* = (a - \rho)/(a + \rho) > 0\) to the offset \(t_1 = 0\). The optimal weights \(w^*\) are shown in Figure 3 for various values of the correlation \(\rho\). For large values of the standardized variance ratio \((a \to \infty)\), the optimal weight tends to \(1/(1+\rho) > 0.5\) such that still the majority of items will be assigned to \(t_2 = 1\). The gain of the optimal design \(\xi^*\) is illustrated in Figure 4 where the efficiency of the optimal design \(\xi_1\) for the fixed effect model \((w_2 = 1)\) and the uniform design \(\xi_2 (w_2 = 1/2)\) is shown, respectively. The efficiency of \(\xi_1\) decreases to \(1 - \rho^2\) when the standardized variance ratio \(a\) tends to infinity, while the efficiency of \(\xi_1\) is increasing from 0.5 for \(a = 0\) to 1 for \(a \to \infty\). Hence, the optimal design \(\xi^*\) substantially outperforms the minimally supported design \(\xi_1\) which is optimal in the fixed effects model if \(a\) becomes large.

A similar phenomenon occurs in the straight line growth model \(\mu_j(\beta) = \beta_0 + \beta_1 t_j\) even in the case of uncorrelated time points. Using the symmetry structure of time reversal as in Lemma 5, we see that for equidistant time points the optimal design \(\xi^*\) is symmetric in time, i.e. it has the form specified in Lemma 5 as long as the covariance matrix \(\Sigma_1\) shares the symmetry property which holds for both the case of compound symmetry as well as the case of autoregressive random effects. In particular, for \(J = 3\) time points, the optimal design has the form \(\xi^* = (I_1^* I_2^* I_3^*)\), where \(I_2^* = I - 2I_1^*\). Hence, optimization has only to be taken with respect to \(I_1^*\). For simplification we consider the situation of uncorrelated random effects which appears as the special case \(\rho = 0\) in either the compound symmetric or the autoregressive case. In terms of weights \(w_j = I_j/I\), the optimal weight \(w_1^*\) also depends only on the standardized variance ratio \(a = I\). By straightforward calculation the optimal weight \(w_1^*\) can be determined as the root of the cubic polynomial \(18a^2w^3 - (20a^2 + 18a)w^2 + 5(a^2 + a)w + a + 1\) in \(0 < w < 1/2\) if \(a \geq 2(\sqrt{2} - 1) \approx 0.8284\), while \(w_1^* = 1/2\) for \(a \leq 2(\sqrt{2} - 1)\). The optimal weight \(w_1^*\) is shown in Figure 5 in dependence on the standardized variance ratio \(a\). From this figure it can be seen that the optimal weight \(w_1^*\) is decreasing in \(a\) for \(a > 2(\sqrt{2} - 1)\), and it tends to \((10 - \sqrt{10})/18 \approx 0.3799\) for \(a \to \infty\). Hence, it can be observed that the optimal design \(\xi^*\) is minimally supported on the endpoints of the time interval for small values of the standardized variance ratio \(a = I\), while for larger values the optimal design is fully supported on all time points.

The efficiency of the minimally supported design \((w_1 = 1/2)\) and of the uniform design \((w_1 = 1/3)\) in Figure 6 show a similar behavior as exhibited in Figure 4 for their counterparts in the ratio model, respectively.

### 4.3 Equivalence Theorem

For fully supported optimal designs, we can derive an equivalence theorem which characterizes optimality in terms of an analytical condition. This result is motivated by the statement in formula (5.2.7) of [Fedorov and Hackl (1997)](p. 78), which covers the situation \(J = p\) as a special case.

**Theorem 1.** Let \(\beta\) be estimable under the design \(\xi^* = (I_1^* \ldots I_J^*)\). Denote by \(\psi_j(\xi)\) the \(j\)th diagonal entry of the \(J \times J\) matrix

\[
(\sigma^2 I_j + \Sigma_1 M_0(\xi))^{-1} A_\beta M_0(\xi)^{-1} A_\beta^T (\sigma^2 I_j + M_0(\xi) \Sigma_1)^{-1},
\]

then \(\xi^*\) is locally \(D\)-optimal if and only if

\[
\psi_j(\xi^*) \geq \frac{1}{J} \sum_{\ell=1}^{J} I^*_\ell \psi_\ell(\xi^*)
\]

for all \(j = 1, \ldots, J\).

Moreover, for the optimal design \(\xi^*\), equality holds in (14) for those \(j\) for which \(I^*_j > 0\).
Figure 5: Optimal weight $w_{1}^{*} = I_{1}^{*}/I$ with respect to $a = I\tau^2$ for the straight line model with uncorrelated random effects, $\rho = 0$, and $J = 3$. The dashed horizontal line indicates the limit $(10 - \sqrt{10})/18 \approx 0.3799$ for $a \to \infty$.

Figure 6: Efficiency of the minimally supported design ($w_1 = 1/2$; solid) and the uniform design ($w_1 = 1/3$; dashed) with respect to $a = I\tau^2$ in the straight line model with uncorrelated random effects, $\rho = 0$, and $J = 3$. 
Table 1: Parameter settings used in the numerical computations

| \( \beta_0 \) | 0 | \( \rho \) | 0, 0.05, \ldots, 0.95 |
| \( \beta_1 \) | 1, 3, 5, 10 | \( \sigma^2_\epsilon \) | 0, 0.1, \ldots, 2, 2.5, 5, 10 |
| \( \beta_2 \) | 0.5, 1, 2 | \( \sigma^2_\gamma \) | 1 |
| \( \beta_3 \) | −2, −1, 0, 1, 2 |

The proof is given in the Appendix. For the general case of potentially not fully supported designs, the essential arguments for proving the equivalence are based on a suggestion by Norbert Gaffke (2022).

The equivalence theorem can be used to check whether numerically obtained designs are indeed optimal as done in the next section. For fully supported designs, the inequalities can be replaced by equations in (14).

**Corollary 1.** Let \( \xi^* \) be fully supported, i.e. \( I_j^* > 0 \) for all \( j \), and let \( A_\beta \) have full column rank \( p \). Let \( \psi_j \) be defined as in Theorem 1. Then \( \xi^* \) is locally \( D \)-optimal if and only if all \( I\psi_j \) are equal, \( j = 1, \ldots, J \).

In the case \( J = p \) of a minimal number of time points, we obtain a characterization of the optimal design which is in accordance with formula (5.2.7) of Fedorov and Hackl (1997), p. 78, when there the regression functions are substituted by the \( j \)th unit vector and the factor \( I \) is introduced to account for the size of the testing.

**Corollary 2.** Let \( J = p \). Denote by \( \psi_j \) the \( j \)th diagonal entry of

\[
M_0(\xi^*)^{-1} \left( \sigma^2_\epsilon M_0(\xi^*)^{-1} + \Sigma_\gamma \right)^{-1} M_0(\xi^*)^{-1}
\]

then \( \xi^* \) is \( D \)-optimal if and only if

\[
I\psi_j = \text{trace} \left( \left( \sigma^2_\epsilon M_0(\xi^*)^{-1} + \Sigma_\gamma \right)^{-1} M_0(\xi^*)^{-1} \right)
\]

for all \( j = 1, \ldots, J \).

In particular, for \( J = p \), the \( D \)-optimal design \( \xi^* \) does neither depend on the location parameters \( \beta \) nor on the particular model for the mean response curve.

### 5 Computational Results

In this section computational results are presented for both nonlinear as well as for the straight line growth curve model considered before. For the linear (straight line growth curve) model the \( D \)-optimal design does not depend on \( \beta \) while for the nonlinear models we determine locally \( D \)-optimal designs for various values of \( \beta \). The values used for the parameter are given in Table 1.

For the reason of expected increase in the mean scores and with respect to standardization, only parameters with \( \beta_1 > \beta_0 = 0 \) were considered. The correlation parameter \( \rho \) and the variance ratio \( \tau^2 = \sigma^2_\gamma / \sigma^2_\epsilon \) were varied to exhibit their influence on the optimal design. All computations where done using R (R Core Team, 2021). The optimality of the designs obtained was checked by applying Theorem 1.

Calculations were made for varying numbers \( J \) of time points and number of items \( I \). Here we only present results for \( J = 7 \) time points, which is motivated by the results of the meta analysis in Scharfen, Jansen and Holling (2018). Computations for other numbers \( J > p \) of time points show similar results. For \( J = p \) the theoretical results of Subsection 4.1 were recovered. Also note, that the figures show results for \( I = 100 \), which seems to be a reasonable number of
Figure 7: Optimal weights \(w^*_j = I^*_j/I\) for the straight line model with \(J = 7\) and \(I = 100\) for different values of \(\tau^2\) and \(\rho\). Compound symmetry black; Autoregressive gray. The dashed horizontal line marks the weight \(1/7\) of the uniform design.

items for \(J = 7\) time points. The subseque nt discussion of the results in the text is in terms of the standardized variance ratio \(a = I\tau^2\). The values \(\tau^2 = 0.1, 0.5, 1\) and \(2\) in the figures correspond to \(a = 10, 50, 100\) and \(200\), respectively.

The general behavior of the optimal weights with respect to the standardized variance ratio \(a = I\tau^2\) and the correlation \(\rho\) is already apparent in the straight line model (see Figure 7). If the standardized variance ratio \(a\) is small, the designs are closer to minimally supported designs which are optimal in the case of no random effects and are uniform on \(p\) time points for the present models. In particular, some weights \(w^*_j = I^*_j/I\) vanish for \(a \to 0\). When \(a\) increases weights are spread out more equally across time points. An explanation for this behavior may be that variance of the random effect is relatively large for large \(a\). Hence, the observations vary more between time points than for small values of \(a\). To get precise estimates this is counteracted in the design by increasing the number of observations spent at those time points. Note, that in the straight line model the weights of the middle points decrease for small \(a\), and the minimally supported optimal design is concentrated on the boundary points \(t_1 = 0\) and \(t_J = J - 1\) only.

As \(\rho\) increases, observations at neighboring time points get more similar and, again, optimal weights of some time points get smaller. For the straight line model these are the interior time points. This qualitative behavior is the same for both covariance structures under consideration. For the autoregressive covariance structure, the weights of time points closer to those of the minimally supported design tend to be higher. Overall the optimal weights under compound symmetry tend to be closer to balanced designs. This is in accordance with the observations for the unstructured model in Subsection 4.2.

For the nonlinear models only asymmetric situations are displayed in Figures 9 to 10 and more weight is spent at the first time points.

For larger slope \(\beta_2\), the weight is concentrated at the first few time points and at the last (Figures 8 and 10 for the exponential model; Figures 9 and 11 for the logistic model). If the slope \(\beta_2\) becomes smaller, more weight is shifted to interior points. (Figure 10 and 11) This is sensible, because initially the mean curve shows its steepest ascent, while at the last time point it is close to the upper asymptote (see Figure 4 for the mean curves. Solid lines correspond to the examples in Figures 8 and 9). For other model parameters than \(\beta_2\) the influence on
Figure 8: Optimal weights $w_j^* = I_j^*/I$ for the exponential model with $\beta = (0 1 1)^T$, $J = 7$, and $I = 100$ for different values of $\tau^2$ and $\rho$. Compound symmetry black; Autoregressive gray. The dashed horizontal line marks the weight $1/7$ of the uniform design.

Figure 9: Optimal weights $w_j^* = I_j^*/I$ for the logistic model with $\beta = (0 1 1 0)^T$, $J = 7$, and $I = 100$ for different values of $\tau^2$ and $\rho$. Compound symmetry black; Autoregressive gray. The dashed horizontal line marks the weight $1/7$ of the uniform design.
Figure 10: Optimal weights $w_j^* = I_j^*/I$ for the exponential model with $\beta = (0 \ 1 \ 0.5)^T$ (left) and $\beta = (0 \ 1 \ 2)^T$ (right), $J = 7$, and $I = 100$ for different values of $\tau$ and $\rho$. Compound symmetry black; Autoregressive gray. The dashed horizontal line marks the weight $1/7$ of the uniform design.

the weights was found to be not substantial in the numerical computations and is, hence, not shown here.

Figure 12 displays the efficiency of the uniform design in dependence on the correlation $\rho$ for different values of the parameters in both the exponential decay model (left panel) and the sigmoid logistic model (right panel). It can be seen from the figures that the efficiency of the uniform design gets smaller for larger values of the correlation $\rho$ and gets larger for larger values of the standardized variance ratio $a = I\tau^2$. The latter behavior is in accordance with the observation that for larger values of $a = I\tau^2$ the observations are more spread over all time points. It is also in agreement with the analytical results exhibited in Figure 6 in the case of a straight line growth curve for $J = 3$ and $\rho = 0$. Moreover, the efficiency of the uniform design is larger for compound symmetry than for the autoregressive case. Over all settings of the computations, the efficiency of the uniform design turns out to be at least 0.72 in the exponential decay and 0.79 in the sigmoid logistic model.

6 Discussion

In this article, we have derived optimal designs for different latent growth models. For linear growth curves, the optimal design only depends on the variances and correlations of the random effects which may be appropriately assumed to be sufficiently known in advance for some studies. In particular, the impact of the variance of the random effect on the optimal design is only through the standardized variance ratio $a = I\sigma^2_\gamma/\sigma^2_\varepsilon$.

When the growth curve is nonlinear in the ability parameters, the determination of optimal designs further requires prior knowledge of the abilities. For most studies, this assumption may be considered as too restrictive. However, adjusting nominal values for the ability parameters leads to locally optimal designs which may serve as a benchmark and as a starting point for the development of designs that require less prior information on the parameters to be estimated. For this aim, three major approaches may come into question: sequential, Bayesian and maximin efficient designs. In the context of retesting, the use of sequential designs is apparently
Figure 11: Optimal weights $w_j^* = I_j^* / I$ for the logistic model with $\beta = (0 \ 1 \ 0.5 \ 0)^T$ (left) and $\beta = (0 \ 1 \ 2 \ 0)^T$ (right), $J = 7$, and $I = 100$ for different values of $\tau^2$ and $\rho$. Compound symmetry black; Autoregressive gray. The dashed horizontal line marks the weight $1/7$ of the uniform design.

Figure 12: Efficiency of the uniform compared to the locally optimal design for $J = 7$ and $I = 100$ with respect to $\rho$ for different values of $\tau^2$. Gray shades change from $\tau^2 = 0.1$ in black, over $\tau^2 = 0.5$ and $\tau^2 = 1$, to $\tau^2 = 2$ in light gray. Solid lines correspond to compound symmetry, dashed lines to autoregressive (left: exponential $\beta = (0 \ 1 \ 1)^T$; right: logistic $\beta = (0 \ 1 \ 1 \ 0)^T$).
difficult because of repeated measurements. However, incorporating prior knowledge on the
abilities within a Bayesian approach may be a promising strategy. There it seems to be quite
reasonable to impose a normal distribution for the ability parameter. Furthermore, maximin
efficient designs are an alternative worth-while considering where the minimal efficiency is maxi-
mized over a range of abilities. In the case of a Rasch model which also includes both an ability
and a difficulty parameter, [Graßhoff et al. (2012)] have successfully developed such maximin
efficient as well as Bayesian optimal designs. Their approach may be adopted to the present
situation.

In the case of a minimal number of time points \(J = p\), the present findings are in accor-
dance with the results for random coefficient regression models, see [Entholzner et al. (2005)],
because the analysis of variance type regression functions of the random effects lie in the space
spanned by the regression functions of the fixed effects (mean response curve). This is no longer
the case if the number \(J\) of time points exceeds the number \(p\) of fixed effects parameters. Then
arguments based on the shape of the fixed effects regression functions do not longer apply and
are superimposed by the properties of the analysis of variance type random effects regression
function which tend to spread observations more uniformly in optimal designs. It would be
challenging to derive general results for such situations in which the random effects are not
directly associated with the fixed effects coefficients.

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Appendix: Proofs

Proof of Lemma 1

First we note that, in the case of fully supported designs ($I_j > 0$ for all $j = 1, \ldots, J$), $M_0$ is of full rank, and the expression on the right hand side of (8) can be obtained by pre- and post-multiplication of (3) by $M_0^{1/2}M_0^{-1/2}$.

In the general case, we make use of the formula $(I + CC^T)^{-1} = I - C(I + C^TC)^{-1}C^T$ for the inverse of a sum of matrices. Let $H$ any matrix such that $H^TH = M_0$ and set $C = \sigma^{-1}_e H\Sigma^{1/2}_\gamma$, where $\Sigma^{1/2}_\gamma$ denotes a symmetric square root of $\Sigma_\gamma$, i.e. $\Sigma_\gamma = \Sigma^{1/2}_\gamma \Sigma^{1/2}_\gamma$. Then we obtain

$$(\sigma^2_e I_m + H\Sigma_\gamma H^T)^{-1} = \frac{1}{\sigma^2_e} \left( I_m - H\Sigma^{1/2}_\gamma (\sigma^2_e I_J + \Sigma^{1/2}_\gamma H^T H\Sigma^{1/2}_\gamma)^{-1} \Sigma^{1/2}_\gamma H^T \right),$$

where $m$ is the number of rows in $H$. From this, we get

$$H^T (\sigma^2_e I_m + H\Sigma_\gamma H^T)^{-1} H = \frac{1}{\sigma^2_e} \left( M_0 - M_0 \Sigma^{1/2}_\gamma (\sigma^2_e I_J + \Sigma^{1/2}_\gamma M_0 \Sigma^{1/2}_\gamma)^{-1} \Sigma^{1/2}_\gamma M_0 \right),$$

irrespective of the particular choice of $H$. If we set $H = F$ or $H = M_0^{1/2}$, we get the left or right hand side in (8), respectively.

Proof of Theorem 1

The $D$-criterion is continuous and concave by Lemma 2. We first start with the situation that the optimal design $\xi^*$ is fully supported and, hence, the information matrix $M_0(\xi^*)$ in the corresponding one-way layout is non-singular. For a fully supported design $\xi = (I_1 \ldots I_J)$,
I_j > 0 for all j = 1, . . . , J}, the directional derivative of log det(M_β(ξ)) at ξ in the direction of another design η = (I_1', . . . , I_J') is given by

\[ \text{trace}\left( M_β(ξ)^{-1} A_β^T (σ^2_ε M_0(ξ)^{-1} + Σ_γ)^{-1} σ^2_ε M_0(ξ)^{-1} (M_0(η) - M_0(ξ)) M_0(ξ)^{-1} \right) \times (σ^2_ε M_0(ξ)^{-1} + Σ_γ)^{-1} A_β \]

\[ = \sum_{j=1}^{J} I_j'ψ_j(ξ) - \sum_{j=1}^{J} I_jψ_j(ξ). \]

As M_β,0 and, hence, the directional derivative is linear in η, the criterion is differentiable. Thus, by standard arguments of convex optimization, it is sufficient to consider the directional derivative for single time point designs η = ξ_j assigning all I observations to a single time point t_j. Then the design ξ* is D-optimal if (and only if) the directional derivative at ξ = ξ_j is less or equal to zero for all η = ξ_j. This is equivalent to the condition that I_jψ_j(ξ*) is less or equal to \( \frac{1}{J} Σ_{j=1}^{J} I_jψ_j(ξ*) \) for all j = 1, . . . , J.

For the general situation, in which the optimal design ξ* may be supported by subset of the time points, we follow an idea proposed by Gaffke (2022) based on the use of subgradients which we sketch here. By Lemma 2 the D-criterion is continuous and concave on the set Ξ_β of all designs for which β is estimable. Hence, − log det(M_β(ξ)) is a “closed proper convex function” in the spirit of Rockafellar (1970). The vector ψ(ξ) = (ψ_1(ξ), . . . , ψ_J(ξ))^T is the gradient at ξ of the D-criterion on the set of fully supported designs and can be continuously extended to Ξ_β by its definition (13).

By Theorem 25.6 in Rockafellar (1970), at not fully supported designs ξ ∈ Ξ_β, the set of subgradients is given by \( \{ ψ(ξ) + v; v ∈ V(ξ)\} \), where V(ξ) is the set of all v = (v_1, . . . , v_J)^T such that v_j = 0 for I_j > 0 and v_j ≥ 0 for I_j = 0. Then, according to Theorem 27.4 in Rockafellar (1970), the design ξ* is D-optimal if and only if there is a vector v ∈ V(ξ) such that \( Σ_{j=1}^{J} I_j(ψ_j(ξ*) + v_j) ≤ Σ_{j=1}^{J} I_j'ψ_j(ξ*) + v_j \) for all designs ξ = (I_1, . . . , I_J). Now, \( Σ_{j=1}^{J} I_jv_j ≥ 0 \) and \( Σ_{j=1}^{J} I_j'v_j = 0 \) for any v ∈ V(ξ). Hence, D-optimality of ξ* is equivalent to \( Σ_{j=1}^{J} I_jψ_j(ξ*) ≤ Σ_{j=1}^{J} I_j'ψ_j(ξ*) \) for all ξ. In the equivalence condition we may again restrict to single time point designs ξ = ξ_j which establishes (14).

Furthermore, for an optimal design ξ* equality follows in (14) for all support points of ξ*.