The Effects of Adaptation on Maximum Likelihood Inference for Non-Linear Models with Normal Errors

Nancy Flournoy*, Caterina May† and Chiara Tommasi‡

*University of Missouri, Columbia, USA
†Università degli Studi del Piemonte Orientale, Italy
‡Università degli Studi di Milano, Italy

Abstract: This work studies the properties of the maximum likelihood estimator (MLE) of a non-linear model with Gaussian errors and multidimensional parameter. The observations are collected in a two-stage experimental design and are dependent since the second stage design is determined by the observations at the first stage; the MLE maximizes the total likelihood. Differently from the most of the literature, the first stage sample size is small, and hence asymptotic approximation is used only in the second stage. It is proved that the MLE is consistent and that its asymptotic distribution is a specific Gaussian mixture, via stable convergence. Finally, a simulation study is provided in the case of a dose-response Emax model.

Keywords: asymptotics, Emax model, Gaussian mixture, maximum likelihood, non-linear regression, small samples, stable convergence, two-stage experimental design

1 Introduction

This paper deals with the problems related to the estimation of a non-linear multi-parameter model with Gaussian errors. Optimal experimental design approach improves the efficiency of the estimate. As well known in the literature (see for instance [1]), when an optimal experimental design is used to estimate the parameter of a non-linear model, the optimal design depends on the unknown parameter. A possibility to tackle this problem is to use a locally optimal design, which is
based on a guessed value for the parameter. If this guessed value is poorly chosen, however, the locally optimal design may be poor too.

One common approach to solve this problem is to adopt a two-stage procedure (see for instance [5], [3], [13]). At the first stage an initial design is applied to collect the first-stage responses which are used to estimate the unknown parameter. This is the so called interim analysis. To collect the second stage responses, a locally optimal design is determined using the estimated parameter from the interim analysis. Finally, the maximum likelihood method is applied to estimate the vector parameter, employing the whole sample of data.

Note that the first and the second stage observations are dependent; the classical approach assumes that both stages have large sample dimensions, and hence the asymptotic theory can be applied, as in [3] and [13]. This approach eliminates the dependency between stages, which is mathematically useful, but not realistic in many applications. In real life problems, in fact, the sample size of the interim analysis can be small. Therefore, in this work we assume that only the second stage sample size goes to infinity while the first stage sample size is fixed, and hence the standard asymptotic behaviour of the maximum likelihood estimator (MLE) does not maintain. The present study extends [10] and [11] which considered a unidimensional parameter and the design at each stage to be a single point; in [11] it is also shown, via simulations, that fixing the first stage sample size improves the limiting approximation; this is an additional reason of the importance of the results here obtained.

Under these assumptions, we prove the consistency of the MLE. Furthermore, we prove that the asymptotic distribution of the MLE is a specific normal mixture; this is obtained via stable convergence (for an overview on stable convergence theory see [8]). In this context of dependent data, the inverse of the Fisher information matrix is not the asymptotic covariance matrix of the MLE. However, we provide an analytical relation between these two quantities, which justifies the idea of using a function of the information matrix as an optimality criterion. Finally, we compare the proposed two-stage adaptive design with a locally optimal design through a simulation study under the Emax model. This study points out that there exist scenarios where the adaptive procedure is superior, although the behaviour is not symmetric with respect to the nominal values of the parameter. A tentative theoretical justification is given, based on the analytical expression of the first order bias term of the first stage MLE.

The paper is organized as follows. Section 2 recalls the basic concept and introduces the model and the notation. Section 3 describes the two-stage adaptive experimental procedure and provides the structure of the likelihood in this partic-
ular case. Section 4 contains the main theoretical results. Section 5 presents an example with simulations. In Section 6 a summary with a few comments conclude the paper.

2 Background and Notation

Assume \( n \) independent observations follow the model

\[
y_j = \eta(x_j, \theta) + \varepsilon_j, \quad \varepsilon_j \sim (0, \sigma^2), \quad j = 1, \ldots, n,
\]

where \( y_j \) is the response of the unit \( j \) treated under an experimental condition \( x_j \in \mathcal{X} \) and \( \eta(x_j, \theta) \) is some possibly non-linear continuous mean function of \( p + 1 \) parameters, \( \theta = (\theta_0, \ldots, \theta_p) \), with \( \theta \in \Theta \), where \( \Theta \) is a compact set in \( \mathbb{R}^{p+1} \). In general, several units may be treated under the same experimental conditions. An experimental design is a finite discrete probability distribution over \( \mathcal{X} \):

\[
\xi = \left\{ x_1, \ldots, x_M \middle| \omega_1, \ldots, \omega_M \right\},
\]

where \( x_m \) denotes the \( m \)th experimental point, or treatment, that may be used in the study and \( \omega_m \) is the proportion of experimental units to be taken at that point; \( \omega_m \geq 0 \) with \( \sum_{m=1}^{M} \omega_m = 1 \), \( m = 1, \ldots, M \) and \( M \) is finite.

It is well known that a good design can substantially improve the inferential results in a statistical analysis. For instance, if the inferential goal is point estimation of \( \theta \), then an optimal design may be chosen to maximize some functional \( \Phi(\cdot) \) of the information matrix

\[
M(\xi; \theta) = \int_{\mathcal{X}} \nabla \eta(x, \theta) \nabla \eta(x, \theta)^T d\xi(x),
\]

as \( M(\xi; \theta)^{-1} \) is proportional to the asymptotic covariance matrix of the maximum likelihood estimator (MLE) ([9]). In other terms, an optimal design for precise estimation of \( \theta \) is

\[
\xi^*(\theta) = \arg \max_{\xi \in \Xi} \Phi[M(\xi; \theta)],
\]

where \( \Xi \) is the set of all the finite discrete probability distributions on \( \mathcal{X} \) (i.e. the set of all designs). Typically, taking derivatives to approximate \( \xi^*(\theta) \) will result in \( \{\omega_m\} \) that are not multiples of \( 1/n \) and they must be adjusted to make them so in order for them to be useful in practice; however, as \( n \) goes to infinity, the
proportion \( n_m/n \) of observations taken at \( x_m \) converges to \( \omega_m \). Some classical references concerning optimal design theory are [6] and [14].

Since the design (4) depends on the unknown parameter \( \theta \) except in the case of linear models, it is said to be \textit{locally optimal} and can be computed only if a guessed value \( \theta_0 \) is available. A locally optimal design is usually not robust with respect to different choices of \( \theta_0 \). To protect against poor choices of \( \theta_0 \), one can use a two stage adaptive procedure where in the first stage \( n_1 \) observations are recruited according to some design and in the second phase additional \( n_2 \) data are observed according to a locally optimal design in which \( \theta \) is estimated from the first stage data. The whole vector of observations (first and second stage data) are then used to estimate \( \theta \) through the maximum likelihood method. The two-stage adaptive design is explained in detail in Section 3.

The properties of a multivariate MLE are studied in Section 4 assuming model (1) in the case that only the second stage sample size goes to infinity; \( n_1 \) is assumed to be finite and small. In many different contexts it is quite common to develop a preliminary small pilot study in order to have an idea about the phenomenon under study and then to perform a larger and well developed study on the same subject. Thus, it is practical to assume that \( n_1 \) is fixed and small, and then asymptotic approximation in the first stage is not adequate.

3 Two-stage adaptive design and corresponding model

Assume that in the first stage a finite number of independent observations, say \( n_1 < +\infty \), are taken according to a design

\[
\xi_1 = \left\{ x_{11}, \ldots, x_{1M_1} \atop \omega_{11}, \ldots, \omega_{1M_1} \right\},
\]

i.e. \( n_{1m} = n_1 \omega_{1m} \) observations are taken at the experimental point \( x_{1m} \), for \( m = 1, \ldots, M_1 \).

Let \( \{y_{1mj}\}_{j=1}^{M_1, n_{1m}} \) be the first stage observations. An estimate for \( \theta \) can be computed maximizing the likelihood corresponding to these first stage observations; the MLE \( \hat{\theta}_{n_1} \) depends on the first stage data through the complete sufficient statistic \( \bar{y}_1 = (\bar{y}_{11}, \ldots, \bar{y}_{1M_1})^T \), where \( \bar{y}_{1m} = \sum_{j=1}^{n_{1m}} y_{1mj}/n_{1m}, m = 1, \ldots, M_1 \); thus, \( \hat{\theta}_{n_1} = \hat{\theta}_{n_1}(\bar{y}_1) \).

In the second stage, \( n_2 \) independent observations are accrued according to the
following local optimum design

\[ \xi^*_2 = \xi^*_2(\hat{\theta}_{n_1}) = \begin{bmatrix} x_{21} \\ \vdots \\ x_{2M_2} \\ \omega_{21} \\ \vdots \\ \omega_{2M_2} \end{bmatrix} ; \quad (5) \]

\{y_{2mj}\}^{M_2,n_{2m}}_{1,1} denotes the second stage observations, where \( n_{2m} \) is obtained by rounding \( n_2\omega_{2m} \) to an integer under the constraint \( \sum_{m=1}^{M_2} n_{2m} = n_2 \), for \( m = 1, \ldots, M_2 \).

Note that \( \xi^*_2 \) is a random probability distribution (discrete and finite) since it depends on the first stage observation through \( \bar{y}_1 \) as \( \hat{\theta}_{n_1} = \hat{\theta}_{n_1}(\bar{y}_1) \); thus, given \( \bar{y}_1 \), the second stage design \( \xi^*_2 \) is determined and \( \{y_{2mj}\}^{M_2,n_{2m}}_{1,1} \) are conditionally independent observations. In addition, it is natural to assume that second stage observations depend on the first stage information only through \( \xi^*_2 \). As a consequence, the observations \( \{y_{imj}\}^{2,M_i,n_{im}}_{1,1,1} \) follow the model

\[ y_{imj} = \eta(x_{im}, \theta) + \varepsilon_{imj}, \quad (6) \]

where, given \( \xi^*_2 \), \( \{y_{2mj}\}^{M_2,n_{2m}}_{1,1} \) are conditionally independent of \( \{y_{1mj}\}^{M_1,n_{1m}}_{1,1} \), and \( \varepsilon_{imj} \) are i.i.d. \( \mathcal{N}(0, \sigma^2) \) for any \( i, m, j \).

### 3.1 Likelihood and the Fisher information matrix

The likelihood for model (6) is

\[ L_n(\theta | \bar{y}_1, \bar{y}_2, x_1, x_2) \propto L_{n_1}(\theta | \bar{y}_1, x_1) \cdot L_{n_2}(\theta | \bar{y}_2, x_2), \quad (7) \]

where \( n = n_1 + n_2 \) and

\[ L_{n_i}(\theta | \bar{y}_i, x_i) \propto \exp \left\{ -\frac{1}{2\sigma^2} \sum_{m=1}^{M_i} n_{im} \left[ \bar{y}_{im} - \eta(x_{im}, \theta) \right]^2 \right\}, \quad i = 1, 2; \]

\( \bar{y}_i = (\bar{y}_{i1}, \ldots, \bar{y}_{iM_i})^T \) and \( \bar{y}_{im} = \frac{1}{n_{im}} \sum_{j=1}^{n_{im}} y_{imj} \) is the stage \( i \) sample mean at the \( m \)-th dose for \( m = 1, \ldots, M_i \).

The total score function is

\[ S_n = \nabla \ln L_n(\theta | \bar{y}_1, \bar{y}_2, x_1, x_2) = S_{1n_1} + S_{2n_2}, \quad (8) \]

where

\[ S_{in_i} = \nabla \ln L_{in_i}(\theta | \bar{y}_i, x_i) = \frac{1}{\sigma^2} \sum_{m=1}^{M_i} n_{im} \left[ \bar{y}_{im} - \eta(x_{im}, \theta) \right] \nabla \eta(x_{im}, \theta) \]
represents the score function for the \( i \)-th stage.

As outlined before, \( \tilde{y}_2 \) depends on \( \tilde{y}_1 \) only through \( \xi_2^* \) and, given \( \tilde{y}_1 \), the second stage design \( \xi_2^* \) is completely determined. As a consequence, \( E_{\tilde{y}_2|\tilde{y}_1}[S_2] = 0 \) and Fisher information matrix is

\[
\text{Cov}_{\tilde{y}_1, \tilde{y}_2}[S_n, S_n^T] = E_{\tilde{y}_1}[S_{1n_1}S_{1n_1}^T] + E_{\tilde{y}_1, \tilde{y}_2}[S_{2n_2}S_{2n_2}^T],
\]

where

\[
E_{\tilde{y}_1}[S_{1n_1}S_{1n_1}^T] = \frac{1}{\sigma^2} \sum_{m=1}^{M_1} n_{1m} \nabla \eta(x_{1m}, \theta) \nabla \eta(x_{1m}, \theta)^T;
\]

\[
E_{\tilde{y}_1, \tilde{y}_2}[S_{2n_2}S_{2n_2}^T] = E_{\tilde{y}_1}E_{\tilde{y}_2|\tilde{y}_1}[S_{2n_2}S_{2n_2}^T];
\]

\[
E_{\tilde{y}_2|\tilde{y}_1}[S_{2n_2}S_{2n_2}^T] = \frac{1}{\sigma^2} \sum_{m=1}^{M_2} n_{2m} \nabla \eta(x_{2m}, \theta) \nabla \eta(x_{2m}, \theta)^T.
\]

Now, the per-subject information can be written as

\[
\frac{1}{n} \text{Cov}_{\tilde{y}_1, \tilde{y}_2}[S_nS_n^T] = \frac{1}{n\sigma^2} \left\{ \sum_{m=1}^{M_1} n_{1m} \nabla \eta(x_{1m}, \theta) \nabla \eta(x_{1m}, \theta)^T \right. \\
\hspace{1cm} + E_{\tilde{y}_1}\left[ \sum_{m=1}^{M_2} n_{2m} \nabla \eta(x_{2m}, \theta) \nabla \eta(x_{2m}, \theta)^T \right] \right\},
\]

where \( M_2, x_{2m} \) and \( n_{2m} \) are random variables, defined by the onto transformation (5) of \( \tilde{y}_1 \).

Note that, as \( n_2 \to \infty \) (and thus \( n \to \infty \)), the per-subject information converges almost surely to

\[
\frac{1}{\sigma^2} E_{\tilde{y}_1} \left[ \int_{\mathcal{X}} \nabla \eta(x, \theta) \nabla \eta(x, \theta)^T d\xi_2^*(x) \right].
\]

4 Asymptotic Properties

One needs an approximation to the asymptotic distribution of the final MLE \( \hat{\theta}_n \) that may be used for inference at the end of the study, where \( n = n_1 + n_2 \) is the total number of observations. The classical approach is to assume that both \( n_1 \) and \( n_2 \) are large (see for instance [13] and [3]). For a closer approximation to many experimental situations, assume here a fixed first stage sample size \( n_1 \) and a large second stage sample size \( n_2 \).
Note that if the experimental conditions in model (1) are taken according to an experimental design $\xi$, then, by the law of large numbers,

$$\frac{1}{n} \sum_{i=1}^{n} \eta(x_i, \theta) \eta(x_i, \theta_1) \xrightarrow{P} \int \eta(x, \theta) \eta(x, \theta_1) d\xi.$$  \hfill (11)

In order to prove the consistency of $\hat{\theta}_n$ assume the following:

A 1 The model is identifiable: if $\theta_1 \neq \theta_2$, then $\eta(x, \theta_1) \neq \eta(x, \theta_2)$.

A 2 The convergence (11) is uniform for all $\theta, \theta_1 \in \Theta$, that is, for any $\delta > 0$,

$$P \left( \sup_{\theta, \theta_1 \in \Theta} \left| \frac{1}{n} \sum_{i=1}^{n} \eta(x_i, \theta) \eta(x_i, \theta_1) - \int \eta(x, \theta) \eta(x, \theta_1) d\xi \right| > \delta \right) \rightarrow 0.$$

Theorem 1 Let $\hat{\theta}_n$ be the MLE maximizing the total likelihood (7). Then

$$\hat{\theta}_n \xrightarrow{P} \theta',$$

where $\theta'$ denotes the true unknown value of $\theta$.

Proof. Observe that $\hat{\theta}_n$ maximizes (7) if and only if it minimizes the average squared errors

$$\mathcal{A}_n(\theta) = \frac{1}{n} \sum_{i=1}^{n1} [y_{i1} - \eta(x_{i1}, \theta)]^2 + \frac{1}{n} \sum_{i=1}^{n2} [y_{i2} - \eta(x_{i2}, \theta)]^2.$$ \hfill (12)

To prove that

$$\sup_{\theta \in \Theta} | \mathcal{A}_n(\theta) - \mathcal{A}(\theta) | \xrightarrow{P} 0,$$ \hfill (13)

where

$$\mathcal{A}(\theta) = \sigma^2 + \int [\eta(x, \theta') - \eta(x, \theta)]^2 d\xi^*_2,$$ \hfill (14)

Rewrite (12) as

$$\mathcal{A}_n(\theta) = \frac{1}{n} \sum_{i=1}^{n1} [y_{i1} - \eta(x_{i1}, \theta)]^2 + \frac{1}{n} \sum_{i=1}^{n2} [y_{i2} - \eta(x_{i2}, \theta') + \eta(x_{i2}, \theta') - \eta(x_{i2}, \theta)]^2$$

$$= A_n(\theta) + B_n(\theta') + C_n(\theta) + D_n(\theta),$$
where

\[ A_n(\theta) = \frac{1}{n} \sum_{i=1}^{n_1} [y_{i1} - \eta(x_{i1}, \theta)]^2; \]

\[ B_n(\theta') = \frac{1}{n} \sum_{i=1}^{n_2} [y_{i2} - \eta(x_{i2}, \theta')]^2; \]

\[ C_n(\theta) = \frac{2}{n} \sum_{i=1}^{n_2} [y_{i2} - \eta(x_{i2}, \theta)][\eta(x_{i2}, \theta') - \eta(x_{i2}, \theta)]; \]

\[ D_n(\theta) = \frac{1}{n} \sum_{i=1}^{n_2} [\eta(x_{i2}, \theta') - \eta(x_{i2}, \theta)]^2. \]

It follows that

1. \( \sup_{\theta \in \Theta} |A_n(\theta)| \xrightarrow{P} 0 \) because \( n_1 \) is finite;

2. \( B_n(\theta') = \frac{1}{n} \sum_{i=1}^{n_2} \varepsilon_{i2}^2 \xrightarrow{P} \sigma^2 \) because the \( \{\varepsilon_{i2}\}_{i=1}^{\infty} \) is a sequence of i.i.d. random variables \( \sim \mathcal{N}(0; \sigma^2); \)

3. The random variables

\[ [y_{i2} - \eta(x_{i2}, \theta')][\eta(x_{i2}, \theta') - \eta(x_{i2}, \theta)] = \varepsilon_{i2}[\eta(x_{i2}, \theta') - \eta(x_{i2}, \theta)]\]

are i.i.d. conditionally on \( \xi_{2*} \) and

\[ E[\varepsilon_{i2}(\eta(x_{i2}, \theta') - \eta(x_{i2}, \theta))]|\xi_{2*} = (\eta(x_{i2}, \theta') - \eta(x_{i2}, \theta))E[\varepsilon_{i2}] = 0. \]

Hence, from the conditional law of large numbers (see, for instance, [12, Theorem 7]) and because \( \eta \) is continuous on the compact set \( \Theta, \)

\[ \sup_{\theta \in \Theta} |C_n(\theta)| \xrightarrow{P} 0. \]

4. Notice that

\[ D_n(\theta) = \frac{1}{n} \sum_{i=1}^{n_2} \eta(x_{i2}, \theta')^2 + \frac{1}{n} \sum_{i=1}^{n_2} \eta(x_{i2}, \theta)^2 - \frac{2}{n} \sum_{i=1}^{n_2} \eta(x_{i2}, \theta')\eta(x_{i2}, \theta); \]

hence, from the conditional law of large numbers and Assumption 2,

\[ P(\sup_{\theta \in \Theta} |D_n(\theta) - D(\theta)| > \delta|\xi_{2*}) \xrightarrow{} 0, \]

8
a.s. for any \( \delta > 0 \), where
\[
D(\theta) = \int \eta(x, \theta')^2 d\xi^*_2 + \int \eta(x_2, \theta)^2 d\xi^*_2 - 2 \int \eta(x_2, \theta') \eta(x_2, \theta) d\xi^*_2 \\
= \int [\eta(x, \theta') - \eta(x, \theta)]^2 d\xi^*_2.
\]

It follows that
\[
E[P(\sup_{\theta \in \Theta} |D_n(\theta) - D(\theta)| > \delta | \xi^*_2)] = P(\sup_{\theta \in \Theta} |D_n(\theta) - D(\theta)| > \delta) \rightarrow 0.
\]

Statement (13) is proved. \( \theta' \) is the unique minimum of \( \mathcal{A}(\theta) \) as a consequence of Assumption 1 and hence the thesis follows.

**Theorem 2** For model (6) with \( \xi^*_2 \) defined in (5) and \( M(\cdot, \cdot) \) defined in (3),
\[
\sqrt{n} \left( \hat{\theta}_n - \theta' \right) \xrightarrow{D} \sigma M(\xi^*_2, \theta')^{-1/2} Z
\]
as \( n_2 \rightarrow \infty \), where \( Z \) is a \((p + 1)\)-dimensional standard normal random vector independent of the random matrix \( M(\xi^*_2, \theta') \).

**Proof.** Let \( S^j_n \) be the \( j \)-the component of the total score function \( S_n \) in (8). From the expansion of \( S_n(\theta) \) around the true value \( \theta' \) we obtain, for any parameter \( j = 0, \ldots, p \),
\[
S^j_n(\hat{\theta}_n) = S^j_{1n_1}(\theta') + S^j_{2n_2}(\theta') + \sum_{k=0}^{p} (\hat{\theta}_{nk} - \theta'_k) \dot{S}^jk_n(\theta') \\
+ \frac{1}{2} \sum_{k=0}^{p} \sum_{l=0}^{p} (\hat{\theta}_{nk} - \theta'_k)(\hat{\theta}_{nl} - \theta'_l) \ddot{S}^jkl_n(\theta^*),
\]
where
\[
\dot{S}^jk_n(\theta) = \frac{\partial^2}{\partial \theta_j \partial \theta_k} \ln \mathcal{L}_{1n_1}(\theta) + \frac{\partial^2}{\partial \theta_j \partial \theta_k} \ln \mathcal{L}_{2n_2}(\theta) = \dot{S}^j_{1n_1}(\theta) + \dot{S}^j_{2n_2}(\theta),
\]
\[
\ddot{S}^jkl_n(\theta) = \frac{\partial^3}{\partial \theta_j \partial \theta_k \partial \theta_l} \ln \mathcal{L}_{1n_1}(\theta) + \frac{\partial^3}{\partial \theta_j \partial \theta_k \partial \theta_l} \ln \mathcal{L}_{2n_2}(\theta) = \ddot{S}^j_{1n_1}(\theta) + \ddot{S}^j_{2n_2}(\theta)
\]
and \( \theta^* \) is a point between \( \hat{\theta}_n \) and \( \theta' \). Since \( S_{2n}^j(\hat{\theta}_n) = 0 \),

\[
\frac{1}{\sqrt{n}} S_{2n}^j(\theta') = -\frac{1}{\sqrt{n}} \left[ S_{1n}^j(\theta') + \sum_{k=0}^{p} (\hat{\theta}_{nk} - \theta'_k) S_{1n}^{jk}(\theta') \right]
- \frac{1}{\sqrt{n}} \left[ \sum_{k=0}^{p} \sum_{l=0}^{p} (\hat{\theta}_{nk} - \theta'_k)(\hat{\theta}_{nl} - \theta'_l) S_{1n}^{jkl}(\theta') \right]
+ \sqrt{n} \sum_{k=0}^{p} (\hat{\theta}_{nk} - \theta'_k) \left[ -\frac{1}{n} S_{2n}^{jk}(\theta') - \frac{1}{2n} \sum_{l=0}^{p} (\hat{\theta}_{nl} - \theta'_l) S_{2n}^{jkl}(\theta^*) \right].
\]

From the consistency proved in Theorem 1, \( S_{2n}^j(\theta') / \sqrt{n} \) is asymptotically equivalent to

\[
\sqrt{n} \sum_{k=0}^{p} (\hat{\theta}_{nk} - \theta'_k) \left[ -\frac{1}{n} S_{2n}^{jk}(\theta') - \frac{1}{2n} \sum_{l=0}^{p} (\hat{\theta}_{nl} - \theta'_l) S_{2n}^{jkl}(\theta^*) \right],
\]

in the sense that their difference converges in probability to zero. In matrix notation, let

\[
\hat{S}_{2n}^j(\theta') = \left\{ \hat{S}_{2n}^{jk}(\theta') \right\}_{(jk)} \quad \text{and} \quad \hat{S}_{2n}^{(l)}(\theta^*) = \left\{ \hat{S}_{2n}^{jkl}(\theta^*) \right\}_{(jk)}, \quad j, k = 0, \ldots, p,
\]

then

\[
\frac{1}{\sqrt{n}} S_{2n}(\theta') \quad \text{and} \quad \left[ -\frac{1}{n} \hat{S}_{2n}^j(\theta') - \frac{1}{2n} \sum_{l=0}^{p} (\hat{\theta}_{nl} - \theta'_l) \hat{S}_{2n}^{jkl}(\theta^*) \right] \sqrt{n} (\hat{\theta}_n - \theta'),
\]

are asymptotically equivalent.

Now,

\[
\frac{1}{\sqrt{n}} S_{2n}(\theta') = \frac{1}{\sigma^2} \frac{1}{\sqrt{n}} \sum_{i=1}^{n_2} \left[ y_{2i} - \eta(x_{2i}, \theta') \right] \nabla \eta(x_{2i}, \theta')
= \frac{1}{\sigma} \frac{1}{\sqrt{n}} \sum_{i=1}^{n_2} \frac{1}{\sigma} \epsilon_{2i} \nabla \eta(x_{2i}, \theta')
\]

(17)

is a zero-mean, square integrable, martingale difference array with respect to the filtration \( \mathcal{F}_0 = \sigma(\bar{y}_1) \), \( \mathcal{F}_1 = \sigma(\bar{y}_1, \epsilon_{21}) \), \ldots, \( \mathcal{F}_{n_2} = \sigma(\bar{y}_1, \epsilon_{21}, \ldots, \epsilon_{2n_2}) \), according to the definition in [7].

10
It follows from [7, Theorem 3.2] that
\[
\frac{1}{\sqrt{n}} \mathbf{S}_{2n_2}(\theta') \xrightarrow{D} \frac{1}{\sigma} M(\xi^*_2, \theta')^{1/2} \mathbf{Z} \quad \text{(stably)} \tag{18}
\]
as \(n_2 \to \infty\), where \(\mathbf{Z}\) is a \((p + 1)\)-dimensional standard normal random vector independent of the random matrix \(M(\xi^*_2, \theta')\). Note that Assumptions 3.18 and 3.20 of [7, Theorem 3.2] are easily verified, while Assumption 3.19 becomes
\[
\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \epsilon_{2i}^2 \nabla \eta(x_{2i}, \theta') \nabla \eta(x_{2m}, \theta')^T \xrightarrow{p} \frac{1}{\sigma^2} M(\xi^*_2, \theta'). \tag{19}
\]
To obtain the (19), the conditional law of large numbers [12, Theorem 7] can be applied: conditional on \(\sigma(\bar{y}_1)\),
\[
\frac{1}{n} \sum_{i=1}^{n} \epsilon_{2i}^2 \nabla \eta(x_{2i}, \theta') \nabla \eta(x_{2i}, \theta')^T \xrightarrow{D} E[\epsilon_{2i}^2 \nabla \eta(x_{2i}, \theta') \nabla \eta(x_{2i}, \theta')^T | \bar{y}_1] = \sigma^2 \int_{\mathcal{X}} \nabla \eta(x, \theta') \nabla \eta(x, \theta')^T d\xi^*_2(x); \tag{20}
\]
averaging on the conditional probability, the convergence (20) maintains also unconditionally.

As a consequence of (18), as shown in [7, (vi) in §3.2], since \(M(\xi^*_2, \theta')\) is \(\mathcal{F}_{n_2}\)-measurable for all \(n_2\),
\[
\sigma M(\xi^*_2, \theta')^{-1/2} \frac{1}{\sqrt{n}} \mathbf{S}_{2n_2}(\theta') \xrightarrow{D} \mathbf{Z}, \tag{21}
\]
where \(\mathbf{Z}\) is a \((p + 1)\)-dimensional standard normal random vector independent of the random matrix \(M(\xi^*_2, \theta')\). Thus, (16) provides that also
\[
Q_n = \sigma M(\xi^*_2, \theta')^{-1/2} \left[ -\frac{1}{n} \dot{\mathbf{S}}_{2n_2}(\theta') - \frac{1}{2n} \sum_{l=0}^{p} (\hat{\theta}_nl - \theta_l) \dot{\mathbf{S}}_{2n_2}^{(l)}(\theta^*) \right] \sqrt{n} \left( \hat{\theta}_n - \theta' \right) \xrightarrow{D} \mathbf{Z}, \tag{22}
\]
from Slutsky’s theorem. Moreover,
\[
-\frac{1}{n} \dot{\mathbf{S}}_{2n_2}(\theta') \xrightarrow{D} \frac{1}{\sigma^2} \sum_{m=1}^{M_2} \omega_{2m} \nabla \eta(x_{2m}, \theta') \nabla \eta(x_{2m}, \theta')^T = \frac{1}{\sigma^2} M(\xi^*_2, \theta') \tag{23}
\]
because the $jk$-th element of the matrix $-\dot{S}_{2n^2}(\theta')/n$ satisfies

$$-\frac{1}{n} S_{2n^2}^{jk}(\theta') = \frac{1}{\sigma^2} \sum_{m=1}^{M_2} n_{2m} \left[ \frac{\partial \eta(x_{2m}, \theta')}{\partial \theta_j} \cdot \frac{\partial \eta(x_{2m}, \theta')}{\partial \theta_k} - \frac{\partial^2 \eta(x_{2m}, \theta')}{\partial \theta_j \partial \theta_k} [\bar{y}_{2m} - \eta(x_{2m}, \theta')] \right]$$

(24)

and the last right term of equation (24) converges in probability to zero by the conditional law of large numbers.

Now,

$$\sqrt{n} (\hat{\theta}_n - \theta') = R_n \cdot Q_n,$$

(25)

where

$$R_n := \left[ -\frac{1}{n} S_{2n^2}(\theta') - \frac{1}{2n} \sum_{l=0}^{p} (\hat{\theta}_n - \theta'_l) S_{2n^2}^{(l)}(\theta') \right]^{-1} \cdot \frac{1}{\sigma} M(\xi_2^*, \theta')^{1/2}. $$

From (23) and from the consistency proved in Theorem 1 (assuming the standard regularity conditions needed for $\frac{1}{n} S_{2n^2}(\theta^*)$ to be bounded in probability),

$$R_n \xrightarrow{p} \sigma M(\xi_2^*, \theta')^{-1/2}. $$

Since the limits in the distributions of $R_n$ and $Q_n$ are independent, $(R_n, Q_n)$ converges to $[\sigma M(\xi_2^*, \theta')^{-1/2}, Z]$, and hence, $R_n \cdot Q_n \xrightarrow{p} \sigma M(\xi_2^*, \theta')^{-1/2} Z$ from Slutsky’s theorem, obtaining the thesis.

**Corollary 1** The asymptotic variance of $\sqrt{n} (\hat{\theta}_n - \theta')$ is

$$\sigma^2 E_{\tilde{\eta}_1} \left[ \left( \int_{\mathcal{X}} \nabla \eta(x, \theta') \nabla \eta(x, \theta')^T d\xi_2^*(x) \right)^{-1} \right]$$

Proof. From (15)

$$\text{AsVar} \left[ \sqrt{n} (\hat{\theta}_n - \theta') \right] = \sigma^2 \cdot \text{Var} \left[ M(\xi_2^*, \theta')^{-1/2} Z \right]$$

$$= \sigma^2 \left\{ \text{Var}_{\tilde{\eta}_1} E_Z \left[ M(\xi_2^*, \theta')^{-1/2} Z \mid \tilde{\eta}_1 \right] \right.\right.$$  

$$+ E_{\tilde{\eta}_1} \text{Var}_Z \left[ M(\xi_2^*, \theta')^{-1/2} Z \mid \tilde{\eta}_1 \right] \right\}. $$

(26)
Since $E_{Z}(Z|\bar{y}_1) = E_{Z}(Z) = 0$, the first term in the brackets of (26) vanishes and in the second term

$$\text{Var}_{\bar{y}_1}E_{Z}\left[M(\xi^*_2, \theta')^{-1/2} Z \mid \bar{y}_1\right] = \text{Var}_{\bar{y}_1}\left[M(\xi^*_2, \theta')^{-1/2} \cdot E_{Z}(Z) \right] = 0.$$ 

Denote by $I$ the identity matrix; taking into account that $\text{Var}_{Z}(Z|\bar{y}_1) = \text{Var}_{Z}(Z) = I$, the second term in (26) is

$$E_{\bar{y}_1}\text{Var}_{Z}\left[M(\xi^*_2, \theta')^{-1/2} Z \mid \bar{y}_1\right] = E_{\bar{y}_1}\left[M(\xi^*_2, \theta')^{-1/2} \text{Var}_{Z}(Z) M(\xi^*_2, \theta')^{-1/2}\right]$$

$$= E_{\bar{y}_1}\left[M(\xi^*_2, \theta')^{-1}\right],$$

and from here the thesis follows.

**Remark.** Compare the asymptotic variance obtained in Corollary 1 with the inverse of (10), to see that the standard equality between the asymptotic variance of the MLE and the inverse of the per-subject information matrix does not maintain in this context. However, the asymptotic variance expression obtained in Corollary 1 justifies choosing a design for the second stage by maximizing a concave function of $M(\xi^*_2, \theta')$ as it is commonly done.

5 Example and simulations: a dose-response model

This section presents a simulation study to compare the two-stage adaptive design with a fixed design in terms of precise estimation.

More specifically, assume that a guessed value $\theta_0 = (\theta_{0,0}, \ldots, \theta_{p,0})$ for $\theta$ is available, for instance from an expert opinion. Initially we take $n_1$ observations according to a locally D-optimal design

$$\xi^*_1(\theta_0) = \begin{pmatrix} x_{11} & \cdots & x_{1M_1} \\ \omega_{11} & \cdots & \omega_{1M_1} \end{pmatrix},$$

and then:

- in the fixed design we add $n_2$ observations according to the same $\xi^*_1(\theta_0)$, independently on the first stage;

- in the adaptive design, instead, add $n_2$ observations according to the locally optimal design (5) (with D-optimality).

In other words, both procedures start with the same fixed optimal design; the fixed continues with this while the adaptive adapts.
5.1 The locally D-optimal design under the Emax model

As an example, simulations are performed under the Emax model, which is well-characterized in the literature and it is frequently used for dose-response designs in clinical trials, as well as in agriculture and in environmental experiments. It has the form (1) with the nonlinear mean function

$$\eta(x, \Theta) = \theta_0 + \theta_1 \frac{x}{x + \theta_2},$$

(27)

where $x \in \mathcal{X} = [a, b]$, $0 \leq a < b$; $\theta_0$ represents the response when the dose is zero; $\theta_1$ is the maximum effect attributable to the drug; and $\theta_2$ is the dose which produces the half of the maximum effect.

The locally D-optimal design $\xi^*_D$ for the Emax model is analytically found in [4]:

$$\xi^*_D(\theta_2) = \left\{ \begin{array}{ccc} a & x^*(\theta_2) & b \\ 1/3 & 1/3 & 1/3 \end{array} \right\},$$

(28)

where the interior support point $x^*(\theta_2)$ is

$$x^*(\theta_2) = \frac{b(a + \theta_2) + a(b + \theta_2)}{(a + \theta_2) + (b + \theta_2)}.$$

(29)

5.2 Simulations of MLEs efficiencies

To compare the precision of the MLEs $\hat{\Theta}_n$ obtained from the fixed and from the adaptive procedures, we compute the corresponding MSEs and their relative efficiency. In these simulations $n_1 = 27$ and $n_2 = 270$. The results are obtained with the $R$ package developed by [2] and are based on 10,000 repetitions. The domain of the non-linear parameter $\theta_2$ is $[0.015; 1500]$ to ensure the existence of the MLE; since $\xi^*_D$ does not depends on $\theta_0$ and $\theta_1$, the true values of the linear parameters are fixed at $\theta^*_0 = 2$ and $\theta^*_1 = 0.467$, as in [3].

Figure 1 display the relative efficiency of the adaptive design with respect to the fixed, for different true values $\theta^*_2 = 25$ and $\theta^*_2 = 50$ and for different nominal values $\theta_{2,0}$, varying on the x-axis around the true value. The standard deviation is assumed to be $\sigma = 0.1, 0.25, 0.5$. To give an idea of the order of magnitude of the MSE, some values are reported in Table 1.
Figure 1: Relative efficiency versus $\theta_{2,0}$ under the Emax model. Relative efficiency is the MSE of $\hat{\theta}_n$ under the adaptive procedure divided by the MSE under the fixed procedure. The vertical line represents the value of $\theta_0' : \theta_0' = 25$ on the left and $\theta_0' : \theta_0' = 50$ on the right.
Parameters | MSE($\hat{\theta}_n$) | Relative Efficiency
--- | --- | ---
$\theta^2_2$ | $\theta_{2,0}$ | $\sigma$ | Fixed | Adaptive | Fix:Adap
25 | 50 | 0.1 | 20.59 | 20.61 | 0.999
25 | 50 | 0.25 | 199.55 | 398.89 | 0.500
25 | 50 | 0.5 | 29094.20 | 50970.56 | 0.571
50 | 25 | 0.1 | 178.30 | 158.95 | 1.122
50 | 25 | 0.25 | 44837.38 | 16634.79 | 2.69
50 | 25 | 0.5 | 327364 | 210367.9 | 1.56
10 | 25 | 0.1 | 2.72 | 2.38 | 1.14
10 | 25 | 0.25 | 18.77 | 38.08 | 0.49
10 | 25 | 0.5 | 1323.66 | 8450.77 | 0.16
25 | 10 | 0.1 | 30.09 | 23.93 | 1.26
25 | 10 | 0.25 | 19106.01 | 321972 | 5.93
25 | 10 | 0.5 | 254911.8 | 92494.97 | 2.76

Table 1: Performance of fixed and adaptive designs

From the simulations, the adaptive design seems to perform better than the fixed one whenever the nominal value $\theta_{2,0}$ is inferior to the true value $\theta^*_2$. These results may be clarified by the following considerations.

Note that, the derivative of $x^*(\theta_2)$ is a positive decreasing function of $\theta_2$ and thus the effect on $x^*(\theta_2)$ is larger for the values $\theta_{2,0} < \theta^*_2$ (see Figure 2). Moreover, the bias of the first stage MLE $\hat{\theta}_{n_1,2}$ is always positive as proved in Proposition 1. Hence, when $\theta_{2,0} < \theta^*_2$ the fixed procedure seems to have a worst performance, while $\hat{\theta}_{n_1,2}$ has a positive bias and thus it takes larger values and we expect that $x^*(\hat{\theta}_{n_1,2})$ is closer to $x^*(\theta^*_2)$ than $x^*(\theta_{2,0})$.

**Proposition 1** If $n_1$ first stage observations are taken according to the D-optimal design (28) with equal numbers treated at $a$, $x^*(\theta_{2,0})$ and $b$, then the bias of the first stage MLE of $\theta_2$ is

$$E(\hat{\theta}_{n_1,2} - \theta_2) = \frac{b_2(\theta)}{n_1} + O(n_1^{-2}),$$
where $b_2(\theta) > 0$ given by

$$
b_2(\theta) = \frac{1}{(a-b)^4\theta_1^2\theta_2^2(a+\theta_2,0)^2(b+\theta_2,0)^2} \cdot \left\{ 3\sigma^2(a+\theta_2)^2(b+\theta_2)^2[2ab+(a+b)\theta_{2,0}+\theta_2(a+b+2\theta_{2,0})]^2 \
[3ab(a+b)+(a^2+10ab+b^2)\theta_{2,0}+3(a+b)\theta_{2,0}^2] \right\}.
$$

(30)

**Proof.** Cox and Snell (1968) introduced the $O(n^{-1})$ formula for the bias of the MLE in the case of $n$ observations not being identically distributed. Cordeiro and Klein (1994) proposed a matrix expression for this bias, which is herein specialized for the Emax model and the D-optimal design $\xi_D^*(\theta_{2,0})$. Calculations are available by the authors upon request.

6 Conclusions

In this paper some important theoretical results about the maximum likelihood estimator are proved when observations are taken from a non linear gaussian model according a two-stage procedure; the model involves a multidimensional parameter. The novelty from the previous literature is that the sample size at the first stage is small and thus standard asymptotic results cannot be applied.
First, the consistency of the MLE is proved under suitable assumptions, commonly satisfied. Then a central limit theorem is obtained, providing a closed form of the asymptotic distribution of the MLE, which is a multivariate Gaussian mixture. As a corollary, the asymptotic covariance is found not to be the inverse of the information matrix as in the standard cases, although they are connected in a specific way.

Finally, as an example, some simulations for the Emax dose-response model are performed to show how the method works. In this case, the exact expression of the first-order bias of the MLE at the first stage is also given. This result suggests, as a future development, some possible bias-corrections of the first stage estimate, that may hopefully improve the proposed two-stage procedure.

Acknowledgments We are grateful to HaiYing Wang, Adam Lane and Giacomo Aletti for their precious comments which helped us to improve this work.

References

[1] A. C. Atkinson, A. N. Donev, and R. D. Tobias. Optimum experimental designs, with SAS, volume 34 of Oxford Statistical Science Series. Oxford University Press, Oxford, 2007.

[2] B. Bornkamp, J. Pinheiro, and F. Bretz. DoseFinding: Planning and Analyzing Dose Finding Experiments, 2018. R package version 0.9-16.

[3] H. Dette, B. Bornkamp, and F. Bretz. On the efficiency of twostage responseadaptive designs. Statistics in Medicine, 32(10):1646–1660, 2012.

[4] H. Dette, C. Kiss, M. Bevanda, and F. Bretz. Optimal designs for the emax, log-linear and exponential models. Biometrika, 97(2):513–518, 2010.

[5] V. Dragalin, V. Fedorov, and Y. Wu. Adaptive designs for selecting drug combinations based on efficacy-toxicity response. Journal of Statistical Planning and Inference, 2:352–373, 2008.

[6] V. Fedorov. Theory of Optimal Experiments. Academic Press, New York, 1972.

[7] P. Hall and C. C. Heyde. Martingale Limit Theory and Its Application. Academic Press, New York, 1980.
[8] E. Häusler and H. Luschgy. *Stable convergence and stable limit theorems*, volume 74 of *Probability Theory and Stochastic Modelling*. Springer, Cham, 2015.

[9] J. Kiefer. General equivalence theory for optimum designs (approximate theory). *The Annals of Statistics*, 2:849–879, 1974.

[10] A. Lane and N. Flournoy. Two-stage adaptive optimal design with fixed first-stage sample size. *Journal of Probability and Statistics*, 2012:1–15, 2012.

[11] A. Lane, P. Yao, and N. Flournoy. Information in a two-stage adaptive optimal design. *Journal of Statistical Planning and Inference*, 144:173–187, 2014.

[12] B. Prakasa Rao. Conditional independence, conditional mixing and conditional association. *Ann. Ist. Stat. Math*, 61:441–460, 2009.

[13] L. Pronzato and A. Pázman. *Design of experiments in nonlinear models*, volume 212 of *Lecture Notes in Statistics*. Springer, New York, 2013. Asymptotic normality, optimality criteria and small-sample properties.

[14] A. Pzman. *Foundations of Optimum Experimental Design*. Springer, Dordrecht, Netherlands, 1986.