Recycled two-stage estimation in nonlinear mixed effects regression models

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Abstract
We consider a re-sampling scheme for estimation of the population parameters in the mixed-effects nonlinear regression models of the type used, for example, in clinical pharmacokinetics. We provide a two-stage estimation procedure which resamples (or recycles), via random weightings, the various parameter’s estimates to construct consistent estimates of their respective sampling distributions. In particular, we establish under rather general distribution-free assumptions, the asymptotic normality and consistency of the standard two-stage estimates and of their resampled version and demonstrate the applicability of our proposed resampling methodology in a small simulation study. A detailed example based on real clinical pharmacokinetic data is also provided.

Keywords Resampling • Random weights • Hierarchical nonlinear models • Random effects

Mathematics Subject Classification MSC code1 • MSC code2 • more

1 Introduction

Hierarchical mixed-effects nonlinear regression models are widely used nowadays to analyze complex data involving longitudinal or repeated measures which are often arising in pharmacokinetics or from medical, biological and other similar applications (see for example Davidian and Giltinan (2003)). In such studies, the sampling units are often “subjects” drawn from the relevant population of interest

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whereby statistical inference, primarily for the estimation of various model
dparameters, is being sought, primarily on certain characteristics of the underlying
population of interest. In that context, the hierarchical nonlinear model can be
considered as an extension of the ordinary nonlinear regression models constructed
to handle and ‘aggregate’ data obtained from several individuals. Modeling this type
of data usually involves a ‘functional’ relationship between at least one predictor
variable, $x$, and the measured response, $y$. As it often the case, the assumed
‘functional’ model between the response $y$ and the predictor $x$, is based on some on
physical or mechanistic grounds and is usually nonlinear in its parameters. For
instance, in pharmacokinetics, a typical (compartmental) model of drug’s concen-
tration in the plasma is obtained from a set differential equations reflecting the
nonlinear time-dependency of the drug’s disposition in the body. Figure 1 below,
illustrates such plasma concentrations profiles for a group of $N = 12$ patients (the
sample), each observed at $n = 11$ time points following the administration of the
drug under study (the Theophylline study, see for example Boeckmann et al. (1994),
Davidian and Giltinan (1995) and also Sect. 5.3 for more details about this well-
known data set).

The primary aim of such pharmacokinetic studies with data as depicted in Fig. 1,
is to make, based on the $N$ patients’ data, generalizations about the drug disposition
in the population of interest to which the group patients belongs. Therefore such
studies require a valid and reliable estimation procedure of the population’s

![Fig. 1 The Theophylline data—drug plasma concentrations (ng/mL) profiles of $N = 12$ patients recorded over time (hr)
“typical and” variability values for each of the underlying pharmacokinetic parameters (e.g.: the ‘typical’ rates of absorption, elimination, and clearance)—usually reflecting the population (hierarchical) distribution of the relevant model’s parameters. In that context, there are three basic types of ‘typical’ population pharmacokinetic parameters. Some are viewed as fixed-effect parameters which quantify the population average kinetics of a drug; others represent inter-individual random-effect parameters, which quantify the typical magnitude of inter-individual variability in pharmacokinetic parameters and the intra-individual random-effect parameter which quantifies the typical magnitude of the intra-individual variability (the experimental error).

The basic hierarchical linear regression model for pharmacokinetics applications was pioneered by Sheiner et al. (1972), which accounted for both types of variations; of within and between subjects. The nonlinear case received widespread attention in later developments. Lindstrom and Bates (1990) proposed a general nonlinear mixed effects model for repeated measures data and proposed estimators combining least squares estimators and maximum likelihood estimators (under specific normality assumption). Vonesh and Carter (1992) discussed nonlinear mixed effects model for unbalanced repeated measures. Additional related references include: Mallet (1986), Davidian and Gallant (1993a); Davidian and Giltinan (1993b, 1995).

In all, the standard approach for inference in hierarchical nonlinear models is typically based on full distributional assumptions for both, the intra-individual and inter-individual random components. The most commonly used assumption is that both random components are considered to be normally distributed. However, this can be a questionable assumption in many cases. Our main results in this work offer a more generalized framework that does not hinge on the normality assumption of the various random terms. In fact, the rigorous asymptotic results we obtained are established only with minimal moments conditions on the random errors and random effect components of the underlying model and thus could be construed as a distribution-free approach.

One simple approach for estimation in such hierarchical ’population’ models is the so-called two-stage estimation method. At the first stage one estimates the ’individual-level’ parameters and then, at the second-stage, combines them in some manner to obtain the ’population-level’ parameter estimates. However despite of its simplicity, the main challenge to such a two-stage estimation approach is in obtaining the sampling distributions and related properties (accuracy, precision, consistency, etc..) of the final estimators, either in finite or in large sample settings. For most part, the performance of these two-stage estimation methods have been evaluated primarily via Monte-Carlo simulations– see related references including: Sheiner and Beal (1981, 1982, 1983), Steimer et al. (1984), and Davidian and Giltinan (1995, 2003). Hence, an alternate and a more data oriented evaluation methodology should be considered in assessing this type of hierarchical models. Using a variant of the random weighting technique, Bar-Lev and Boukai (2015) proposed a re-sampling scheme, which is termed herein recycling, as a valuable and valid alternative methodology for evaluation and comparison of the estimation procedure. Zhang and Boukai (2019b) studied the validity and established the
asymptotic consistency and asymptotic normality of the recycled estimates in a one-layered nonlinear regression model.

In the present paper we extend Bar-Lev and Boukai (2015) approach to include general random weights in the case of hierarchical nonlinear regression models with minimal moments assumptions on the random error-terms/effects. In Sect. 2, we present the basic framework for the hierarchical nonlinear regression models with fixed and random effects. In Sect. 3, we describe the Standard Two-Stage (STS) estimation procedure for the population parameters appropriate in this hierarchical nonlinear regression settings. Along these lines, we introduce a corresponding re-sampling scheme especially devised, based on general random weights, to obtain the recycled version of the STS estimators. In Sect. 4, we establish the asymptotic consistency and asymptotic normality of the STS estimators in such general settings. As we mentioned before, our rigorous results do not depend on specifying the distribution(s) of the random component terms in the model (both errors and effects), but rather, are obtained largely based on minimal moments assumptions. As far as we know, these are the first provably valid asymptotic results concerning the sampling distribution and implied sampling properties of the estimators obtained using the STS procedure in the context of hierarchical nonlinear regression. In addition, we demonstrate the applicability via the asymptotic consistency and normality of the recycled version of the STS estimators. These results enable us to use the sampling distribution of the recycled version of the STS estimators to approximate the unknown sampling distribution of the actual STS estimators in a general ’distribution-free’ framework. The results of extensive simulation studies and a detailed application to the Theophylline data are provided in Sect. 5. The proofs of our main results along with many other technical details are provided in the “Appendix”.

2 The basic hierarchical (population) model

Consider a study involving a random sample of N individuals, where the nonlinear regression model (as in Zhang and Boukai (2019b)) is assumed to hold for each of the i-th individuals. That is, for each i, (i = 1, 2, ..., N), we have available the n_i (repeated) observations on the response variable in the form of \( y_i := (y_{i1}, y_{i2}, \ldots, y_{in_i})^t \), where

\[
y_{ij} = f(x_{ij}; \theta_i) + \epsilon_{ij}, \quad j = 1, \ldots, n_i,
\]

and \( x_{ij} \) is the j-th covariate for the i-th individual, which gives rise to the response, \( y_{ij} \), for \( j = 1, \ldots, n_i \) and \( i = 1, \ldots, N \). Here, \( f(\cdot) \) is a given nonlinear function and \( \epsilon_{ij} \) denote some i.i.d. \( (0, \sigma^2) \) error-terms. That is, if we set \( \epsilon_i := (\epsilon_{i1}, \epsilon_{i2}, \ldots, \epsilon_{in_i})^t \), then \( E(\epsilon_i) = 0 \) and \( \text{Var}(\epsilon_i) = \text{Cov}(\epsilon_i\epsilon_i^t) = \sigma^2 I_{n_i} \). In the current context of hierarchical modeling, the parameter vector \( \theta_i = (\theta_{i1}, \theta_{i2}, \ldots, \theta_{ip})^t \in \Theta \subset \mathbb{R}^p \), (with \( p < n_i \)), can vary from individual to individual, so that \( \theta_i \) is seen as the individual-specific realization of \( \theta \). More specifically, it is assumed that, independent of the error terms, \( \epsilon_i \).
\[ \theta_i := \theta_0 + b_i, \]  

where \( \theta_0 := (\theta_{01}, \theta_{02}, \ldots, \theta_{0p})^t \) is a fixed population parameter, though unknown, and \( b_i = (b_{i1}, b_{i2}, \ldots, b_{ip})^t \) is a \( p \times 1 \) vector representing the random effects associated with \( i \)-th individual. It is assumed that the random effects, \( b_1, b_2, \ldots, b_N \) are independent and identically distributed random vectors satisfying,

\[ E(b_i) = 0 \quad \text{and} \quad \text{Var}(b_i) \equiv \text{Cov}(b_i, b'_i) = D. \]

Here \( \sigma^2 \) represents the within individual variability and \( D \) describes the between individuals variability. Thus, \( \theta_1, \theta_2, \ldots, \theta_N \) are i.i.d. random vectors with

\[ E(\theta_i) = 0 \quad \text{and} \quad \text{Var}(\theta_i) = D. \]

In the simple (i.e.: standard) hierarchical modeling it is often assumed that \( D \) is some diagonal matrix of the form \( D = \text{Diag}(\lambda^2_1, \lambda^2_2, \ldots, \lambda^2_p) \) or even simpler, as \( D = \lambda^2 I_p \) for some \( \lambda > 0 \), and that \( \text{Var}(\epsilon_i) = \sigma^2 I_n_i \) for each \( i = 1, \ldots, N \) for some \( \sigma > 0 \).

In the more complex hierarchical modeling, more general structures of the within individual variability \( \text{Var}(\epsilon_i) = \Gamma_i \) (for some \( \Gamma_i \)) and of the between individuals variability, \( D \), are possible. However, even in the simplest structure, the available estimation methods for these model’s parameters, \( \theta_0, \sigma^2 \) and \( D \) are typically highly iterative in their nature and are based on the variations of the least squares estimation. Similarly, even when considered under some specific distributional assumptions, such as that both, the error terms \( \epsilon_i \), and the random effects \( b_i \) are normally distributed, so that, \( \epsilon_i \sim \mathcal{N}_{n_i}(0, \sigma^2 I_{n_i}) \) and \( b_i \sim \mathcal{N}_p(\mathbf{0}, D) \), for each \( i = 1, \ldots, N \). In fact, many of the available results in the literature hinge on the specific normality assumption and on the ability to effectively ’linearize’ the regression function \( f(\cdot) \) (see for example Bates and Watts (2007)) in order to obtain some assessment of the resulting sampling distributions for the parameters’ estimates. We point out that here we require no specific distributional assumptions (such as normality, or otherwise) on either the intra-individual and the inter-individual error terms, \( \epsilon_i \) nor \( b_i \), respectively.

### 3 The two-stage estimation procedure

For each \( i = 1, \ldots, N \), let \( f_i(\theta) \) denote the \( n_i \times 1 \) vectors whose elements are \( f(x_{ij}, \theta), j = 1, \ldots, n_i \) then model (1) can be written more succinctly as

\[ y_i = f_i(\theta_i) + \epsilon_i \]

Accordingly, the STS estimation procedure can be described as follows:
On Stage I: For each $i = 1, \ldots, N$ obtain $\hat{h}_{ni}$ as the minimizer of

$$Q_i(\theta) := (y_i - f_i(\theta))(y_i - f_i(\theta))^t \equiv \sum_{j=1}^{n_i} (y_{ij} - f(x_{ij}, \theta))^2,$$

so as to form $\hat{h}_{n1}, \hat{h}_{n2}, \ldots, \hat{h}_{nN}$, based on all the $M := \sum_{i=1}^N n_i$ available observations. Next, estimate the within-individual variability component, $\sigma^2$, by

$$\hat{\sigma}^2_M := \frac{1}{M - pN} \sum_{i=1}^N Q_i(\hat{h}_{ni}).$$

On Stage II: Estimate the 'population' parameter $\theta_0$ by the average

$$\hat{\theta} - STS := \frac{1}{N} \sum_{i=1}^N \hat{h}_{ni}. \tag{5}$$

Next, estimate $\text{Var}(\hat{\theta} - STS)$ by $S^2 - STS/N$, where

$$S^2 - STS := \sum_{i=1}^N (\hat{h}_{ni} - \hat{\theta} - STS)(\hat{h}_{ni} - \hat{\theta} - STS)^t.$$

Finally estimate the between-individual variability component, $D$, by

$$\hat{D} = S^2 - STS - \min(\hat{\nu}, \hat{\sigma}^2_M) \hat{\Sigma}_N,$$  \tag{6}

where $\hat{\Sigma}_N := \frac{1}{N} \sum_{i=1}^N \Sigma_{ni}(\hat{\theta}_{ni})$, with $\Sigma_{ni}^{-1}$ defined as,

$$\Sigma_{ni}^{-1}(\theta) := \frac{1}{n} \sum_{i=1}^{n_i} \nabla f_i(\theta) \nabla f_i(\theta)^t, \tag{7}$$

and where $\hat{\nu}$ is the smallest root of the equation $|S^2 - STS - \nu \hat{\Sigma}_N| = 0$, see Davidian and Giltinan (2003) for details.

Bar-Lev and Boukai (2015) provided a numerical study of this two-stage estimation procedure in the context of a (hierarchical) pharmacokinetics modeling under the normality assumption. They also proposed a corresponding two-stage resampling scheme based on specific Dirichlet($I$) random weights. However, in this paper we consider a more general framework for the random weights to be used.

As in Zhang and Boukai (2019b), we let for each $n \geq 1$, the random weights, $w_n = (w_{1,n}, w_{2,n}, \ldots, w_{n,n})^t$, be a vector of exchangeable nonnegative random variables with $E(w_{i,n}) = 1$ and $\text{Var}(w_{i,n}) := \tau_n^2$, and let $W_i \equiv W_{1,n} = (w_{i,n} - 1)/\tau_n$ be the standardized version of $w_{i,n}, i = 1, \ldots, n$. In addition we also assume:

**Assumption W** The underlying distribution of the random weights $w_n$ satisfies

1. For all $n \geq 1$, the random weights $w_n$ are independent of $(\epsilon_1, \epsilon_2, \ldots, \epsilon_n)^t$,
\[ \tau_n^2 = o(n), \ E(W_iW_j) = O(n^{-1}) \quad \text{and} \quad E(W_i^2W_j^2) \to 1 \quad \text{for all} \ i \neq j, \ E(W_i^4) < \infty \quad \text{for all} \ i. \]

Some examples of random weights, \( w_n \) that satisfy the above conditions in Assumption W are: the Multinomial weights, \( w_n \sim \text{Multinomial}(n, 1/n, 1/n, \ldots, 1/n) \), which correspond to the classical bootstrap of Efron (1979) and the Dirichlet weights, \( w_n \equiv n \times z_n \) where \( z_n \sim \text{Dirichlet}(\alpha, \alpha, \ldots, \alpha) \), with \( \alpha > 0 \) which often refer to as the Bayesian bootstrap (see Rubin (1981), and its variants as in Zheng and Tu (1988) and Lo (1991)).

We will assume throughout this paper that all the random weights we use in the sequel do satisfy Assumption W. With such random weights \( w_n \) at hand, we define in similarity to (3), the \textit{recycled} version \( \hat{\theta}_n^* \) of \( \hat{\theta}_n \) as the minimizer of the \textit{randomly weighted} least squares criterion. With such general random weights, the \textit{recycled} version of the STS estimation procedure described in (4-7) above is:

\textbf{On Stage I} For each \( i = 1, \ldots, N \), independently generate random weights, \( w_i = (w_{i1}, w_{i2}, \ldots, w_{in})^t \) that satisfy Assumption W with \( \text{Var}(w_{ij}) = \tau_{ni}^2 \) and obtain \( \hat{\theta}_{ni}^* \) as the minimizer of

\[ Q_i^*(\theta) := \sum_{j=1}^{n_i} w_{ij}(y_{ij} - f(x_{ij}, \theta))^2, \tag{8} \]

so as to form \( \hat{\theta}_{n1}^*, \hat{\theta}_{n2}^*, \ldots, \hat{\theta}_{nN}^* \).

\textbf{On Stage II} Independent of \textbf{Stage I}, generate random weights, \( u = (u_1, u_2, \ldots, u_N)^t \) that satisfy Assumption W with \( \text{Var}(u_i) = \tau_{N}^2 \), and obtained the \textit{recycled} version of \( \hat{\theta} - \text{STS} \) as:

\[ \hat{\theta} - \text{RTS}^* := \frac{1}{N} \sum_{i=1}^{N} u_i \hat{\theta}_{ni}^* \tag{9} \]

The \textit{recycled} version \( D^* \) of \( D \) can be subsequently obtained as described in \textbf{Stage II} above.

\section*{4 Consistency of the STS and the recycled estimation procedures}

In this section we present some asymptotic results that establish and validate the consistency and asymptotic normality of the STS estimator, \( \hat{\theta} - \text{STS} \) (Theorems 1 and 2) and of its \textit{recycled} version \( \hat{\theta} - \text{RTS}^* \) (Theorems 3 and 4), obtained using the general random weights satisfying the premises of Assumption W. We establish these results without the 'typical' normality assumption on the \textit{within-individual} error terms, \( \epsilon_{ij} \), nor on the \textit{between-individual} random effects \( b_i \). However, for
simplicity of the exposition, we state these results in the case of \( p = 1 \), so that \( \Theta \in \mathbb{R} \). With that in mind, we denote for each \( i = 1, \ldots, N \),
\[
f_{ij}(\theta) \equiv f(x_{ij}, \theta), \quad \text{for } j = 1, \ldots, n_i.
\]

Accordingly, the least squares criterion in (1), becomes
\[
Q_n(\theta) := \sum_{j=1}^{n_i} (y_{ij} - f_{ij}(\theta))^2,
\]
and the LS estimator \( \hat{\theta}_{ni} \) is readily seen as the solution of
\[
Q_{ni}'(\theta) := 2 \sum_{j=1}^{n_i} \phi_{ij}(\theta) = 0
\tag{10}
\]
where,
\[
\phi_{ij}(\theta) := -(y_{ij} - f_{ij}(\theta)) f'_{ij}(\theta),
\tag{11}
\]
with \( f'_{ij}(\theta) := df_{ij}(\theta)/d\theta \), for \( j = 1, \ldots, n_i \) and for each \( i = 1, \ldots, N \). We write \( f''_{ij}(\theta) := df'_{ij}(\theta)/d\theta \) and \( \phi''_{ij}(\theta) := d\phi'_{ij}(\theta)/d\theta \), etc. As in Zhang and Boukai (2019b), we also assume that \( f'_{ij}(\theta) \) and \( f''_{ij}(\theta) \) exist for all \( \theta \) near \( \theta_0 \). However, to account for the inclusion of the \((0, \lambda^2)\) random effect term, \( b_i \), in the model, we also assume that,

**Assumption A**

For each \( i = 1, \ldots, N \)
1. \( a_{ni}^2 := \sigma^2 \sum_{j=1}^{n_i} E(f_{ij}''(\theta_0 + b_i)) \to \infty \text{ as } n_i \to \infty, ; \)
2. \( \lim \sup_{n_i \to \infty} a_{ni}^{-2} \sum_{j=1}^{n_i} \sup_{|\theta - \theta_0 - b_i| \leq \delta} f_{ij}''(\theta) < \infty \)
3. \( a_{ni}^{-2} \sum_{j=1}^{n_i} f_{ij}''(\theta) \to \frac{1}{\sigma^2} \text{ uniformly in } |\theta - \theta_0 - b_i| \leq \delta. \)

In the following two Theorems we establish, under the conditions of Assumption A, the asymptotic consistency and normality of \( \hat{\theta}_{STS} \). Their proofs and some related technical results are given in Sect. 7.1.

**Theorem 1** Suppose that Assumption A holds, then there exists a sequence \( \hat{\theta}_{ni} \) of solutions of (10) such that \( \hat{\theta}_{ni} = \theta_0 + b_i + a_{ni}^{-1}T_{ni} \), where \( |T_{ni}| < K \) in probability, for each \( i = 1, 2, \ldots, N \). Further, there exists a sequence \( \hat{\theta}_{STS} \) as expressed in (5) such that \( \hat{\theta}_{STS} - \theta_0 \to^p 0 \), as \( n_i \to \infty \), for \( i = 1, 2, \ldots, N \), and as \( N \to \infty \).

**Theorem 2** Suppose that Assumption A holds. If \( \lim_{N, n_i \to \infty} N/a_{ni}^2 < \infty \), for all \( i = 1, 2, \ldots, N \), then there exists a sequence \( \hat{\theta}_{STS} \) as expressed in (5) such that \( \hat{\theta} - STS - \theta_0 = \frac{1}{N} \sum_{i=1}^{N} b_i - \psi - N, n_i \), where \( \sqrt{N} \psi - N, n_i \to^p 0 \). Further,
\[ R_N^\ast := \frac{\sqrt{N}}{\lambda} (\hat{\theta} - \text{STS} - \theta_0) \Rightarrow \mathcal{N}(0, 1) \]

as \( n_i \to \infty \), for \( i = 1, 2, \ldots, N \), and as \( N \to \infty \).

For the \textit{recycled} STS estimation procedure as described in Sect. 3, the \textit{recycled} version \( \hat{\theta}_{ni}^\ast \) of \( \hat{\theta}_{ni} \) is the minimizer of \( (8) \), or alternatively, the direct solution of

\[
Q_i''(\theta) := 2 \sum_{j=1}^{n_i} w_{ij} \phi_{ij}(\theta) = 0, \tag{12}
\]

where \( w_i = (w_{i1}, w_{i2}, \ldots, w_{in_i})^t \) are the randomly drawn weights (satisfying Assumption W), for the \( i \)th individual, \( i = 1, 2, \ldots, N \). For establishing comparable results to those given in Theorems 1 and 2 for the \textit{recycled} version, \( \hat{\theta}^\ast - \text{RTS} = \sum_{i=1}^{N} u_i \hat{\theta}_{ni}^\ast / N \) of \( \hat{\theta} - \text{STS} = \sum_{i=1}^{N} \hat{\theta}_{ni} / N \), with the random weights \( u = (u_1, u_2, \ldots, u_N)^t \) as in \textit{Stage II *}, we need the following additional assumptions.

**Assumption B** In addition to Assumption A, we assume that \( E(e_{ij}^4) < \infty \) and that for each \( i = 1, 2, \ldots, N \),

1. \( \limsup_{n_i \to \infty} a_i^{-2} \sum_{j=1}^{n_i} \sup_{|\theta - \theta_{0} - b_j| \leq \delta} f_{ij}''(\theta) < \infty \),
2. \( \limsup_{n_i \to \infty} a_i^{-2} \sum_{j=1}^{n_i} \sup_{|\theta - \theta_{0} - b_j| \leq \delta} f_{ij}''(\theta) < \infty \),
3. As \( n_i \to \infty, n_i a_i^{-2} \to c_i \geq 0 \).

In Theorems 3 and 4 below we establish, under the conditions of Assumptions A and B, the asymptotic consistency and normality of the \textit{recycled} estimator \( \hat{\theta}^\ast - \text{RTS} \). Their proofs and some related technical results are given in Sect. 7.2.

**Theorem 3** Suppose that Assumptions A and B hold. Then there exists a sequence \( \hat{\theta}_{ni}^\ast \) as the solution of \( (12) \) such that \( \hat{\theta}_{ni}^\ast = \hat{\theta}_{ni} + a_i^{-1}T_{ni}^\ast \), where \( |T_{ni}^\ast| < K \tau_{ni} \) in probability, for \( i = 1, \ldots, N \). Further for any \( \epsilon > 0 \), we have \( P(\hat{\theta}^\ast - \text{RTS} - \theta_0 \geq \epsilon) = o_p(1) \), as \( n_i \to \infty \), for \( i = 1, 2, \ldots, N \), and as \( N \to \infty \).

**Theorem 4** Suppose that Assumptions A and B hold. If for each \( i = 1, 2, \ldots, N \), \( \frac{\tau_{ni}}{\tau - N} = o(\sqrt{N}) \), then we have \( \hat{\theta}^\ast_{\text{RTS}} - \hat{\theta}^\ast_{\text{STS}} = \frac{1}{N} \sum_{i=1}^{N} (u_i - 1) \hat{\theta}_{ni} - \psi^\ast_{N,n_i} \), where \( \frac{\sqrt{N}}{\tau N} \psi^\ast_{N,n_i} \to 0 \) as \( N, n_i \to \infty \). Additionally,

\[
R_N^\ast := \frac{\sqrt{N}}{\lambda \tau N} (\hat{\theta}^\ast_{\text{RTS}} - \hat{\theta}^\ast_{\text{STS}}) \Rightarrow \mathcal{N}(0, 1),
\]

as \( n_i \to \infty \), for \( i = 1, 2, \ldots, N \), and as \( N \to \infty \).

The proofs of Theorems 3 and 4 and some related technical results are given in Sect. 7.1. The following Corollary is an immediate consequence of the above.
results. It suggests that the sampling distribution of $\hat{\theta}_{\text{STS}}$ can be well approximated by that of the recycled or re-sampled version of it, $\hat{\theta}_{\text{RTS}}$.

**Corollary 1** For all $t \in \mathbb{R}$, let $\mathcal{H}_N(t) = P(R_N \leq t)$, and $\mathcal{H}_N^*(t) = P^*(R_N^* \leq t)$, denote the corresponding c.d.f of $R_N$ and $R_N^*$, respectively. Then by Theorems 2 and 4,

$$\sup_t |\mathcal{H}_n^*(t) - \mathcal{H}_n(t)| \to 0 \quad \text{in probability.}$$

5 Implementation and numerical results

5.1 Illustrating the STS estimation procedure

To illustrate the main results of Sect. 4 for the hierarchical nonlinear regression model and the corresponding STS estimation procedure as described in (4-7) above, we consider a typical compartmental modeling from pharmacokinetics. In the standard two-compartment model, the relationship between the measure drug concentration and the post-dosage time $t$, (following an intravenous administration), can be described through the nonlinear function of the form:

$$f(t; \theta) = \eta_1 e^{-\eta_2 t} + \eta_3 e^{-\eta_4 t}, \quad (13)$$

with $\eta := (\eta_1, \eta_2, \eta_3, \eta_4)^\top$ being a parameter representing the various kinetics rate constants, such as the rate of elimination, rate of absorption, clearance, volume, etc. Since these constants (i.e. parameters) must be positive, we re-parametrize the model with $\theta \equiv \log(\eta)$ (with $\theta_k = \log(\eta_k)$, $k = 1, 2, 3, 4$), so that with $t > 0$,

$$f(t; \theta) = \exp(\theta_1)\exp\{-\exp(\theta_2) t\} + \exp(\theta_3)\exp\{-\exp(\theta_4) t\}, \quad (14)$$

with $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)^\top \in \mathbb{R}^4$. For the simulation study we consider a situation in which the (plasma) drug concentrations $\{y_{ij}\}$ of $N$ individuals were measured at post-dosage times $t_{ij}$ and are related as in model (1) via the nonlinear regression model,

$$y_{ij} = f(t_{ij}; \theta_i) + \epsilon_{ij},$$

for $j = 1, \ldots, n_i$ and $i = 1, \ldots, N$. Here, as in Sect. 4, $\epsilon_{ij}$ are standard i.i.d. $(0, \sigma^2)$ random error terms and $\theta_i = \theta_0 + b_i$, where $b_i$ are independent identically distributed random effects terms, with mean $0$ and unknown variance $\lambda^2 I_{4 \times 4}$. Accordingly, we have in all a total of 6 unknown parameters, namely, $\theta_0 = (\theta_{10}, \theta_{20}, \theta_{30}, \theta_{40})^\top$, $\sigma$ and $\lambda$.

Since $\sigma$ and $\lambda$ represent variation within and between individuals (respectively), different setting for these two lead to very different situations. For instance, Fig. 2a below, depicts the situation for $N = 5$ and $n_i \equiv n = 15$, each, when $\sigma = 0.1$ and $\lambda = 0.1$, so that the variation between individuals are similar to variation within individuals. Figure 2b depicts the situation with $\sigma = 0.05, \lambda = 1$, so that the variation between individuals is much larger than variation within individuals.
For the simulation, we set $h_0 = \left(1, 0.8, -0.5, -1\right)^t$, and for each $i$, the times $t_{ij}, j = 1, \ldots, n$ were generated uniformly from $[0, 8]$ interval. To allow for different ‘distributions’, the error terms, $\varepsilon_{ij}$, as well as the random effect terms, $b_i$, were generated either from the (a) Truncated Normal, (b) Normal and (c) Laplace distributions – all in consideration of Assumption A in our main results.

For each simulation run, with the Truncated Normal distribution for the error-terms and the random effects terms, we calculated the value of $\hat{h}_{STS}^k$ as an estimator of $h_0$ and repeated this procedure $M = 1000$ times to calculate the corresponding Mean Square Error (MSE) as followed,

$$MSE = \frac{1}{M} \sum_{k=1}^{M} \|\hat{h}_{STS}^k - h_0\|^2$$

The corresponding simulation results obtained for various values of $N$ and $n$, are presented in Table 1 for $\sigma = 0.1, \lambda = 1$ and $\sigma = 0.05, \lambda = 1$.

**Table 1** The MSE of STS estimates for truncated Normal error-terms/effects with $\sigma = 0.1, \lambda = 1$ and $\sigma = 0.05, \lambda = 1$

| $n$ | $\sigma = 0.1, \lambda = 1$ | $\sigma = 0.05, \lambda = 1$ |
|-----|-----------------|-----------------|
|     | $N = 15$ | $N = 15$ | $N = 30$ | $N = 30$ | $N = 50$ | $N = 50$ | $N = 100$ | $N = 100$ | $N = 200$ | $N = 200$ |
| 15  | 0.8662 | 0.8662 | 0.2289 | 0.2289 | 0.0465 | 0.0465 | 0.0114 | 0.0114 | 0.0063 | 0.0063 |
| 30  | 0.5767 | 0.5767 | 0.1071 | 0.1071 | 0.0244 | 0.0244 | 0.0057 | 0.0057 | 0.0033 | 0.0033 |
| 50  | 0.4584 | 0.4584 | 0.0893 | 0.0893 | 0.0210 | 0.0210 | 0.0038 | 0.0038 | 0.0020 | 0.0020 |
| 100 | 0.3785 | 0.3785 | 0.0692 | 0.0692 | 0.0125 | 0.0125 | 0.0022 | 0.0022 | 0.0010 | 0.0010 |
| 200 | 0.3506 | 0.3506 | 0.0590 | 0.0590 | 0.0089 | 0.0089 | 0.0014 | 0.0014 | 0.0006 | 0.0006 |
From Table 1, we see that with \( n \) and \( N \) both increasing, the MSE is decreasing, as expected. However, when \( \sigma = 0.05, \lambda = 1, n \) increasing for a fixed \( N \), doesn’t contribute to smaller MSE, which is consistent with our main result Theorem 1, the STS estimate is not consistent with only \( n_i \to \infty \), (this effect is more obvious in the case \( \lambda \) is relatively large).

For simulating the results of Theorem 2, we choose \( \theta_2 \) to be the unknown parameter, and use the main result to construct 95% Confidence Interval as

\[
\left( \hat{\theta}_{STS} - 1.96 \sqrt{N}, \hat{\theta}_{STS} + 1.96 \sqrt{N} \right),
\]

where

\[
\hat{\lambda}^2 = \frac{1}{N - 1} \sum_{i=1}^{N} (\hat{\theta}_i - \hat{\theta}_{STS})^2.
\]

The estimate for \( \hat{\lambda} \) used here is the simple STS estimate, not the corrected one as in (6). 1,000 replications of such simulations were executed to determine the percentage of times the true value of the parameter estimates was contained in the interval. We use \( \sigma = 0.5, \lambda = 0.5 \) and observed Coverage Percentages are provided in Table 2.

From these results we can observe that with \( n \) and \( N \) both increase, the Coverage Percentage approximate to 0.95. While when \( n \) is small (15), with \( N \) increase, the Coverage Percentage is drifting farther away from the desired level of 0.95. This finding is consistent with our main result, the convergence require the condition \( \lim_{N, n_i \to \infty} N/a_{ni}^2 < \infty \), which in this case becomes \( \lim_{n \to \infty} 1/n a_n^2/\sigma^2 < \infty \), that is \( \lim_{N \to \infty} N/n < \infty \) is required. Hence, when \( N \) is much large than \( n \), this condition does not hold. Although for this model, error terms that follow the normal distribution do not satisfy Assumption A, we used normal error terms in the simulations, and reported the resulting MSE and Coverage Percentage for 95% confidence interval in Tables 2 and 3. From the results we can observe that with

| n  | truncated Normal | Normal |
|----|------------------|--------|
|    | 15  | 30  | 50  | 100 | 200 | 15  | 30  | 50  | 100 | 200 |
| 15  | 0.903 | 0.934 | 0.933 | 0.931 | 0.931 | 0.918 | 0.927 | 0.939 | 0.951 | 0.922 |
| 30  | 0.896 | 0.940 | 0.940 | 0.943 | 0.944 | 0.901 | 0.939 | 0.944 | 0.931 | 0.932 |
| 50  | 0.883 | 0.941 | 0.959 | 0.944 | 0.944 | 0.871 | 0.947 | 0.949 | 0.950 | 0.944 |
| 100 | 0.828 | 0.948 | 0.946 | 0.941 | 0.944 | 0.851 | 0.950 | 0.934 | 0.949 | 0.948 |
| 200 | 0.759 | 0.943 | 0.932 | 0.935 | 0.949 | 0.740 | 0.949 | 0.944 | 0.951 | 0.945 |
n and N increasing, the MSE are smaller and Coverage Percentage are closer to 0.95.

We further considered simulations using the Laplace distributions for the error terms and random effects terms. The complete results are reported in Zhang and Boukai (2019b) and indicate of similar conclusions.

5.2 Illustrating the recycled STS estimation procedure

Here we provide the results of the simulation studies corresponding to Theorem 3 and 4 concerning the recycled STS estimator, $\hat{θ}^{STS}_{RTS}$. We considered the same nonlinear (compartmental) model as given in the previous subsection, however again with $p = 1$. Accordingly, we choose $θ_2$ to represent the model’s unknown parameter and set, for the simulations, $θ_0 = 0.8$, for each $i$. As before, we generated the values of $\{t_{ij}, j = 1, \ldots, n\}$ uniformly from the $[0, 8]$ interval, and drew the error terms, $ε_{ij}$ and the random effects terms, $b_i$, from the truncated Normal distribution.

For each simulation run, we calculated the value of $\hat{θ}_{STS}$ as in Sect. 3, then with $B = 1,000$, we generated $B \times N$ independent replications of the random weights $w_i = (w_{i1}, w_{i2}, \ldots, w_{in})$ and $B = 1,000$ independent replications of the random weight $u = (u_1, u_2, \ldots, u_N)$, to obtain $\hat{θ}_{STS}^1, \hat{θ}_{STS}^2, \ldots, \hat{θ}_{STS}^B$. The correspond 95% Confidence Intervals were formed. With $σ = 1, \lambda = 1$ a total of $M = 2000$ replications of such simulations were executed to determine the percentage of times the true value of the parameter estimates was contained in the interval and average confidence interval length was calculated. The Coverage Percentages with average confidence interval lengths are reported in Tables 4 and 5.

Table 4 demonstrates the results of the asymptotic results of Sect. 4. Table 5 provide Coverage Percentages with average confidence interval lengths, with random weights set to be Multinomial, Dirichlet or Exponential distributed. From these results we can see with $N$ and $n$ both increase, the Coverage Percentages converges to 0.95 as expected (see Corollary 5). Also notice that Coverage Percentages derived from the recycled STS are more accurate (closer to 0.95) than the asymptotic result, especially when $n$ and $N$ are small.

We further consider the case when $n$ is even smaller. Table 6 provides Coverage Percentages and the average confidence interval length when $n = 10$ for the case of the Multinomial, Dirichlet or Exponential distributed random weights. As can be seen, in these cases, our procedure produces reasonable results. However, we must
point out that the effects of a small sample size on our procedure depend also on the
dimensionality, \( p \), of the parameter \( \theta \), on the “nature” of the non-linear regression
function \( f_i(\cdot) \) and its gradients, and on the particular minimization (optimization)
algorithm used on \( Q_i(\theta) \) in (4) and on \( Q^*(\theta) \) in (8). Clearly, further numerical
experimentation could be instructive in these regards.
5.3 An example—theophylline data

We illustrate our proposed recycled two-stage estimation procedure with the Theophylline data set (which is widely available as Theoph under the R package, R Core Team (2020)). This well-known data set provides the concentration-time profiles (see Fig. 1) as were obtained in the pharmacokinetic study of the anti-asthmatic agent Theophylline, and reported by Boeckmann et al. (1994) and subsequently analyzed by Davidian and Giltinan (1995) (NLME), Kurada and Chen (2018) (NLMIXED) as well as in Adeniyi et al. (2018). In this experiment, the drug was administered orally to \( N = 12 \) subjects, and serum concentrations were measured at 11 time points per subject over the subsequent 25 hours. However, as in Davidian and Giltinan (1995), we also excluded here the zero time point from the analysis to simplify the modeling of the within-subject mean variance relationship.

For the analysis, a one-compartment version of the model in (13) in which \( g_1 = /C_0 \) was fitted to the data. The resulting pharmacokinetic model is described by the three parameters \( \theta_i = (/K_{a_i}, /K_{e_i}, /C_{i})' \), (with \( /K_{a_i} > /K_{e_i} \)), representing the absorption rate (1/hr), the elimination rate (1/hr) and fundamental clearance (L/hr), per each of the \( N \) individual under study. Often however, the model parametrization is given in term of the compartmental volume, \( V \), where \( V = /C_{l}/K_{e} \) (L). Thus, the mean concentration at time \( t_{ij} \), \( (i = 1, \ldots, N, j = 1, \ldots, n) \), following a single dose of size \( d_0 \) administrated at time \( t_{i1} \), by the \( i \)-th individual, \( (i = 1, \ldots, N) \), is,

\[
 f(t_{ij}; \theta_i) = \frac{d_0 /K_{a_i} /K_{e_i}}{/C_{l}(/K_{a_i} - /K_{e_i})} (\exp(-/K_{e_i}t_{ij}) - \exp(-/K_{a_i}t_{ij})). \tag{15}
\]

The statistical model accounts for the errors intervening between true and the observed drug concentrations, and with the inter-individual variability in the model’s parameters. To deal with the first, it is assumed that for each \( i = 1, ..., N \),

\[
 y_{ij} = f(t_{ij}; \theta_i) + \epsilon_{ij}
\]

where \( y_{ij} \) is the observed \( j^{th} \) drug concentration of the \( i^{th} \) individual, obtained at time \( t_{ij} \), and where \( \epsilon_{ij} \) are some i.i.d random error terms with mean 0 and variance \( \sigma^2_{\epsilon} \). Here \( \sigma^2_{\epsilon} \) is assumed to be the only intra-individual random effect parameter of concern. Similarly, for modeling the inter-individual variability in the parameters, we assume that \( \beta_i := log(\theta_i) \equiv (/K_{a_i}, /K_{e_i}, /C_{l})' \), represent some random effects with \( E(\beta_i) = \beta_0 \equiv (/K_{a0}, /K_{e0}, /C_{l0})' \) and where \( Var(\beta_i) = \mathbf{D} = \text{diag}(\sigma^2_{/K_{a}}, \sigma^2_{/K_{e}}, \sigma^2_{/C_{l}}) \), for each \( i = 1, ..., N \). Accordingly, \( \theta_0 \equiv exp(\beta_0) = (/K_{a0}, /K_{e0}, /C_{l0})' \) represents the fixed-effect population parameter. In all, there are seven population parameters, namely: \( /K_{a0}, /K_{e0}, /C_{l0} \) and \( \sigma^2_{/K_{a}}, \sigma^2_{/K_{e}}, \sigma^2_{/C_{l}} \) and \( \sigma_\epsilon \). Because of the logarithmic scale, all these standard deviations are dimensionless quantities and they may be regarded as approximate coefficients of variation. We emphasize that, unlike the other cited approaches (namely NLME and NLMIXED), our modeling here does not depend on any specific distributional assumption (i.e. normality) for the random effects, \( \beta_i \) nor for the error terms \( \epsilon_i \).
In fact, after standardization to a unit dose, (so that $d_0 = 1$ in (15)) the data on each individual may be viewed as consisting of 10 observations. Using the Dirichlet weights in $B = 1000$ iterations, we obtained the recycled two-stage estimates $\hat{\theta} - RTS^*$ of $\theta_0 = E(\theta_1)$ as well as the STS estimates, $\hat{\theta} - STS$ for these data. The results are presented in Table 7, which also provides the estimates for the variance components in $D$ and in $D^*$, as well as the 95% confidence intervals for the fixed parameters $K_e0, K_a0$ and $Cl_0$ as where obtained directly from the corresponding recycled sampling distributions. For sake of comparison, we also provide in Table 8 the results of NLME estimation procedure as in Lindstrom and Bates (1990) (using nlme R package) and those obtained from the NLMIXED estimation procedure as was reported by Kurada and Chen (2018). We point out again that, while the results in Tables 7 and 8 are largely similar, the estimation procedures utilized in Table 8 (NLME and NLMIXED) hinge on the normality assumptions for the random effect terms (both within and between). In contrast, the result presented in Table 7 using our recycled two-stage estimation procedure are entirely free of such specific distributional assumptions.

### 6 Summary and discussion

We considered the general random weights approach as a viable re-sampling technique in the case of hierarchical nonlinear regression models involving fixed and random effects. We revisit the Standard Two-Stage (STS) estimation procedure for the population parameters, say $\theta_0$, appropriate in this hierarchical nonlinear regression settings. While intuitively appealing, this STS approach was studied in the literature primarily via simulations and with an underlying normality assumption. Here, we establish at first the asymptotic consistency and the asymptotic normality of the STS estimator, $\hat{\theta} - STS$, in the more general context. Our rigorous results, as stated in Theorems 1 and 2, do not hinge on any specific distributional assumptions (e.g., normality) on the random component terms in the model (both errors-terms and random effects), but rather, they are obtained largely

| Parameter | $K_a$ (hr$^{-1}$) | $K_e$ (hr$^{-1}$) | $Cl$ (L/hr) | $\sigma^2$ |
|-----------|-----------------|-----------------|-------------|-----------|
| $\hat{\theta} - STS$ | 1.610 | 0.088 | 0.040 | 0.022 |
| $\hat{\theta} - RTS^*$ | 1.639 | 0.089 | 0.040 | 0.017 |
| $D_{ii}$ | 0.588 | 0.039 | 0.082 |
| $D_{i'}^*$ | 0.649 | 0.051 | 0.085 |
| 95%CI | (1.070, 2.513) | (0.078, 0.099) | (0.034, 0.046) |

Table 7 The Recycled STS estimation from the PK-data on Theophylline
based on minimal moments assumptions. Next, we presented the recycled (or the re-sampled) version, $\hat{\theta} - RTS^*$, of the STS estimates, $\hat{\theta} - STS$, in this hierarchical nonlinear regression context and established its applicability under general random weighting scheme (Assumption W). In Theorems 3 and 4 we established, the consistency and asymptotic normality of the corresponding re-sampled estimator, $\hat{\theta} - RTS^*$. These results enable us to use the recycled sampling distribution $\hat{\theta} - RTS^*$, as is generated by the re-sampling procedure using the random weights technique to approximate the actual, though unknown, sampling distribution of the STS estimator, $\hat{\theta} - STS$ (see Corollary 5). Thereby allowing us to validly assess the sampling properties of $\hat{\theta} - STS$, such as precision and coverage probabilities based on the re-sampled (via the random weights) data. Toward that end, we augmented our rigorous theoretical results with a detailed simulation study (covering various sample sizes) illustrating the properties of the estimators, $\hat{\theta} - STS$ and $\hat{\theta} - RTS^*$ under various scenarios involving normal as well as non-normal error terms and utilizing different choices of random weights (Multinomial, Dirichlet and Exponential). Clearly, the effects of the choice of random weights on the numeral minimization (optimization) procedures used by various software, will depend also on the non-linear regression function, its curvatures and the number of data points used. However, this choice could be instructed by experimentation. Additionally, we provided a detailed application of our two-stage recycled estimation procedure to the data of the Theophylline study, and provided a comparison with the (normality-based) estimation procedures, NLME and NLMIXED. This real-data example, with $N = 12$ and $n = 10$, also illustrates the applicability of our approach even to data involving small sample sizes. In any case, we believe that the gamut of results presented here, both theoretical and numerical, are indicative of the potential and promise of the random weighting recycled (re-sampled) STS estimation procedure method to other more complex hierarchical non-linear regression models involving more structured mixed-effects parameters. For instance, extension to cases in which (2) is generalized to $\theta_i = A_i \theta_0 + B_i b_i$, where: $A_i$, $B_i$ are some design matrices. However, for sake of scope and space, this and other related issues will have to be pursued elsewhere.

### Table 8 Estimation Result of the PK-data on Theophylline using NLME and NLMIXED (published) procedures

| Parameter | $K_a$ (hr$^{-1}$) | $K_e$ (hr$^{-1}$) | CI (L/hr) |
|-----------|------------------|------------------|-----------|
| **NLMIXED est.** | 1.617            | 0.086            | 0.040     |
| 95%CI      | (1.038, 2.519)   | (0.076, 0.096)   | (0.035, 0.045) |
| **NLME est.** | 1.571            | 0.088            | 0.040     |
| 95%CI      | (1.069, 2.306)   | (0.078, 0.099)   | (0.034, 0.047) |
In this section of the “Appendix” we provide the technical results needed for the proofs of Theorems 1 and 2 on the STS estimator $\hat{\theta}_{STS}$ in the hierarchical nonlinear regression model. In the sequel, we let $\phi_{1ij}(\theta) := \phi'_{ij}(\theta)$ (see (11)), and set $K$ to denote a generic constant. Recall that (see Assumption A(1)),

$$a_n^2 := \sigma^2 \sum_{j=1}^{n_i} E(f_{ij}^2(\theta_0 + b_i)) \to \infty \text{ as } n_i \to \infty.$$ 

**Lemma 1** Under the conditions of Assumption A, for some $K > 0$

$$a_n^{-2} \sup_{|i| \leq K} \sum_{j=1}^{n_i} \phi_{1ij}(b_{i1}) - \frac{1}{\sigma^2} \to 0 \text{ a.s.,}$$

where $b_{i1} := b_{i1n}(t)$ is a sequence such that $\sup_{|i| \leq K} |b_{i1} - b_i - \theta_0| \to 0$, a.s., as $n_i \to \infty$.

**Proof of Lemma 1** Since $\phi_{1ij}(\theta) := \phi'_{ij}(\theta)$, we have

$$\phi_{1ij}(\theta) \equiv f_{ij}^2(\theta) - \epsilon_{iji}f_{ij}''(\theta) - (f_{ij}(\theta_0 + b_i) - f_{ij}(\theta))f_{ij}''(\theta).$$

Accordingly, we first note that,

$$\left| a_n^{-2} \sup_{|i| \leq K} \sum_{j=1}^{n_i} \phi_{1ij}(b_{i1}) - \frac{1}{\sigma^2} \right| \leq \left| a_n^{-2} \sup_{|i| \leq K} \sum_{j=1}^{n_i} f_{ij}^2(b_{i1}) - \frac{1}{\sigma^2} \right|$$

$$+ a_n^{-2} \sup_{|i| \leq K} \left| \sum_{j=1}^{n_i} \epsilon_{iji} f_{ij}''(b_{i1}) \right|$$

$$+ a_n^{-2} \sup_{|i| \leq K} \left| \sum_{j=1}^{n_i} (f_{ij}(\theta_0 + b_i) - f_{ij}(b_{i1}))f_{ij}''(b_{i1}) \right|.$$ 

By Assumption A (3), we have $a_n^{-2} \sup_{|i| \leq K} \sum_{j=1}^{n_i} f_{ij}^2(b_{i1}) - \frac{1}{\sigma^2} \to 0$ a.s., and by Assumption A (2) and Corollary A in Wu (1981), we also have,

$$a_n^{-2} \sup_{|i| \leq K} \left| \sum_{j=1}^{n_i} \epsilon_{iji} f_{ij}''(b_{i1}) \right| \to 0 \text{ a.s.}.$$ 

Finally, the last term converge to 0 a.s. by Assumption A, an application of Cauchy-Schwarz inequality and Corollary A in Wu (1981). Thus we have
Similarly,

\[ a_n^{-2} \sup_{|j| \leq K} \sum_{j=1}^{n_i} \phi_{ij}(b_{ij}) - \frac{1}{\sigma^2} \to 0 \ a.s.. \]

\[ \square \]

**Lemma 2** Let \( X_i \) be a sequence of random variables bounded in probability and let \( Y_i \) be a sequence of random variables which satisfies \( \frac{1}{n} \sum_{i=1}^{n} |Y_i| \to 0 \) in probability. Then \( \frac{1}{n} \sum_{i=1}^{n} X_i Y_i \to 0. \)

**Proof of Lemma 2** Since \( X_i \) is bounded in probability, for any \( \epsilon > 0 \), there is \( K_\epsilon \) such that for any \( i \), \( P(|X_i| > K_\epsilon) < \epsilon. \) Then

\[
\lim_{n \to \infty} P(|\frac{1}{n} \sum_{i=1}^{n} X_i Y_i| > \epsilon) = \lim_{n \to \infty} \left[ P(|\frac{1}{n} \sum_{i=1}^{n} X_i Y_i| > \epsilon, |X_i| < K_\epsilon) \right] \\
+ \lim_{n \to \infty} \left[ P(|\frac{1}{n} \sum_{i=1}^{n} X_i Y_i| > \epsilon, |X_i| > K_\epsilon) \right] \\
\leq \lim_{n \to \infty} P\left(|\frac{1}{n} \sum_{i=1}^{n} \frac{X_i}{K_\epsilon} Y_i| > \frac{\epsilon}{K_\epsilon}, |X_i| < K_\epsilon\right) + \epsilon \\
\leq \lim_{n \to \infty} P\left(|\frac{1}{n} \sum_{i=1}^{n} \frac{Y_i}{K_\epsilon}| > \frac{\epsilon}{K_\epsilon}, |X_i| < K_\epsilon\right) + \epsilon = \epsilon,
\]

from which the desired result follows. \( \square \)

**Lemma 3** There exists a \( K > 0 \) such that for any \( \epsilon > 0 \), for any \( i \),

\[
P\left[ a_n^{-1} \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \right] > K \right] < \frac{\epsilon}{2}.
\]

**Proof of Lemma 3** Since \( \epsilon_{ij} \) and \( b_i \) are independent, for each \( i = 1, \ldots, N \), we have that for any \( j_1 \neq j_2 \),

\[
E(\phi_{ij}(\theta_0 + b_i)) = E[E(\phi_{ij}(\theta_0 + b_i)|b_i)] \\
= E[E(\epsilon_{ij}, f'_{ij}(\theta_0 + b_i))] \\
= E[\epsilon_{ij} f'_{ij}(\theta_0 + b_i)] \\
= 0.
\]

Similarly,

\[
E(\phi_{ij}(\theta_0 + b_i)) = E[E(\epsilon_{ij} f'_{ij}(\theta_0 + b_i)|b_i)] = E[E(\epsilon_{ij} f'_{ij}(\theta_0 + b_i)) = 0.
\]

Hence, we have, \( E(\phi_{ij}(\theta_0 + b_i)) = E(\phi_{ij}(\theta_0 + b_i))E(\phi_{ij}(\theta_0 + b_i)). \)

To conclude that,
\[ \text{Var} \left( \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \right) = \sum_{j=1}^{n_i} \text{Var}(\phi_{ij}(\theta_0 + b_i)) \]
\[ = \sum_{j=1}^{n_i} \text{Var}(\epsilon_{ij}f_{ij}(\theta_0 + b_i)) \]
\[ = \sum_{j=1}^{n_i} E(\epsilon_{ij}^2)E(f_{ij}^2(\theta_0 + b_i)) \]
\[ = \sigma^2 \sum_{j=1}^{n_i} E(f_{ij}^2(\theta_0 + b_i)) \equiv a_n^2. \]

Accordingly, there exists a \( K > 0 \) such that for any \( \epsilon > 0 \), for any \( i \),
\[ P \left[ \left| a_n^{-1} \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \right| > K \right] < \frac{\epsilon}{2}. \]

We are now ready to prove Theorem 1

**Proof of Theorem 1** Let
\[ S_n(t) := a_n^{-1} \sum_{j=1}^{n_i} \left[ \phi_{ij}(\theta_0 + b_i + a_n^{-1}t) - \phi_{ij}(\theta_0 + b_i) \right] - \frac{t}{\sigma^2}, \quad (16) \]

Next we will show for any given constant \( K \),
\[ \sup_{|t| \leq K} |S_n(t)| \rightarrow 0 \quad a.s. \quad (17) \]

By a Taylor expansion, \( \phi_{ij}(\theta_0 + b_i + a_n^{-1}t) = \phi_{ij}(\theta_0 + b_i) + \phi_{1ij}(b_{i1})a_n^{-1}t \), where \( b_{i1} = \theta_0 + b_i + ca_n^{-1}t \) for some \( 0 < c < 1 \). Accordingly we obtain that,
\[ \sup_{|t| \leq K} |S_n(t)| = \sup_{|t| \leq K} a_n^{-1} \sum_{j=1}^{n_i} \phi_{1ij}(b_{i1})a_n^{-1}t - \frac{t}{\sigma^2} \]
\[ = K a_n^{-2} \sup_{|t| \leq K} \sum_{j=1}^{n_i} \phi_{1ij}(b_{i1}) - \frac{1}{\sigma^2}. \]

By Lemma 1, \( a_n^{-2} \sup_{|t| \leq K} \sum_{j=1}^{n_i} \phi_{1ij}(b_{i1}) - \frac{1}{\sigma^2} \rightarrow 0 \quad a.s. \) Thus, we have proved (17).

Next, by (16),
\[ A_n(t) := a_n^{-1} t \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i + a_n^{-1}t) = tS_n(t) + a_n^{-1} t \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) + \frac{t^2}{\sigma^2}. \]

Thus,
\[
\inf_{|t|=K} A_n(t) \geq -K \sup_{|t|=K} |S_n(t)| - Ka_n^{-1} \left| \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \right| + \frac{K^2}{\sigma^2}.
\]

By lemma 3 there exists a \( K > 0 \) such that for any \( \epsilon > 0 \), for any \( i \),

\[
P\left[ a_n^{-1} \left| \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \right| > K \right] < \frac{\epsilon}{2}. \tag{18}
\]

So that by (18) and (17) we may choose \( K \) large enough such that for sufficiently large \( n_i \),

\[
P\left( \inf_{|t|=K} A_n(t) \geq 0 \right) \geq P\left( \sup_{|t|=K} |S_n(t)| + a_n^{-1} \left| \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \right| \leq \frac{K}{\sigma^2} \right)
\]

\[
= 1 - P\left( \sup_{|t|=K} |S_n(t)| + a_n^{-1} \left| \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \right| > \frac{K}{\sigma^2} \right)
\]

\[
\geq 1 - P\left( \sup_{|t|=K} |S_n(t)| > \frac{K}{4\sigma^2} - P\left( \left| \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \right| > \frac{K}{4\sigma^2} \right) \right)
\]

\[
\geq 1 - \epsilon.
\]

By the continuity of \( \sum_{j=1}^{n_i} \phi_{ij}(\theta) \) in \( \theta \), we have, for sufficiently large \( n_i \), that there exists a constant \( K \) such that the equation

\[
\sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i + a_n^{-1} t) = 0,
\]

has a root \( t = T_{ni} \) in \( |t| \leq K \) with probability larger than \( 1 - \epsilon \). That is, we have \( \hat{\theta}_{ni} = \theta_0 + b_i + a_n^{-1} T_{ni} \), where \( |T_{ni}| < K \) in probability. Thus, by Lemma 2,

\[
\hat{\theta}_{STS} - \theta_0 = \frac{1}{N} \sum_{i=1}^{N} b_i + \frac{1}{N} \sum_{i=1}^{N} a_n^{-1} T_{ni} \xrightarrow{p} 0.
\]

\( \square \)

For establishing the asymptotic normality result as stated in Theorem 2, we need the following Lemma.

**Lemma 4** Under the conditions of Assumptions A,

\[
\frac{1}{\sqrt{N}} \sum_{i=1}^{N} a_n^{-2} \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \xrightarrow{p} 0.
\]
Proof of Lemma 4 Let $X_{ni} := a_{ni}^{-1} \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i)$, where, by proof of Theorem 1 we have $E(X_{ni}) = 0$ and $Var(X_{ni}) = 1$. Thus,

$$\frac{1}{\sqrt{N}} \sum_{i=1}^{N} a_{ni}^{-2} \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) = \frac{1}{\sqrt{N}} \sum_{i=1}^{N} a_{ni}^{-1} X_{ni}.$$ 

Now, for any $\epsilon > 0$,

$$P\left( \left| \frac{1}{\sqrt{N}} \sum_{i=1}^{N} a_{ni}^{-1} X_{ni} \right| > \epsilon \right) \leq \frac{\sum_{i=1}^{N} \frac{1}{a_{wi}^2}}{N\epsilon^2} \to 0.$$ 

Accordingly, we have $\frac{1}{\sqrt{N}} \sum_{i=1}^{N} a_{ni}^{-2} \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \overset{p}{\to} 0$, as required. \hfill \qed

Proof of Theorem 2 We first note that by Lemma 1 and (16),

$$\hat{\theta}_{ni} - \theta_0 - b_i = -a_{ni}^{-2} \sigma^2 \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) - a_{ni}^{-1} \sigma^2 S_{ni}(T_{ni}).$$

Thus,

$$\hat{\theta}_{STS} - \theta_0 = \frac{1}{N} \sum_{i=1}^{N} b_i - \frac{\sigma^2}{N} \sum_{i=1}^{N} a_{ni}^{-2} \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) - \frac{\sigma^2}{N} \sum_{i=1}^{N} a_{ni}^{-1} S_{ni}(T_{ni}).$$

Recall that $\sum_{i=1}^{N} b_i / N \to E(b_1) \equiv 0$. In view of (17) and since $\lim_{N,ni \to \infty} N/a_{ni}^2 < \infty$, we have

$$\frac{\sigma^2}{\sqrt{N}} \sum_{i=1}^{N} a_{ni}^{-1} S_{ni}(T_{ni}) \to 0 \text{ a.s..}$$

Finally, from Lemma 4,

$$\frac{1}{\sqrt{N}} \sum_{i=1}^{N} a_{ni}^{-2} \sum_{j=1}^{n_i} \phi_{ij}(\theta_0 + b_i) \overset{p}{\to} 0.$$ 

Thus, it follows that $\lambda^{-1} \sqrt{N}(\hat{\theta}_{STS} - \theta_0) \Rightarrow \mathcal{N}(0, 1)$. \hfill \qed

7.2. Technical details and proofs, the recycled STS estimation case

In this section of the “Appendix” we provide the technical results needed for the proofs of Theorems 3 and 4 on the recycled STS estimator, $\hat{\theta}_{RTS}$, in the hierarchical nonlinear regression model. We begin with a re-statement of Lemma 2 from Boukai and Zhang (2018) which is concerned with the general random weights under Assumption W.
Lemma 5 Let $\mathbf{w}_n = (w_{1:n}, w_{1:n}, \ldots, w_{n:n})^t$ be random weights that satisfy the conditions of Assumption W. Then with $W_i = (w_{i:n} - 1)/\tau_n$, $i = 1, \ldots, n$ and $\bar{W}_n := \frac{1}{n} \sum_{i=1}^{n} W_i$ we have, as $n \to \infty$, that (i) $\frac{1}{n} \sum_{i=1}^{n} W_i \to^n 0$ (ii) $\frac{1}{n} \sum_{i=1}^{n} W_i^2 \to 1$ and hence (iii) $\frac{1}{n} \sum_{i=1}^{n} (W_i - \bar{W}_n)^2 \to^n 1$.

Lemma 6 Under the conditions of Assumption W, $\frac{1}{n} \sum_{i=1}^{n} w_{i:n} - 1 \to^n 0$. Further, let $\mathbf{u}_n = (u_1, u_2, \ldots, u_n)^t$ denote a vector of $n$ i.i.d. random variables that is independent of $\mathbf{w}_n$ with $E(u_i) = 0, E(u_i^2) < \infty$. Then, conditional on the given value of the $\mathbf{u}_n$, we have $\frac{1}{n} \sum_{i=1}^{n} u_i w_{i:n} \to^n 0$, as $n \to \infty$.

Proof of Lemma 6 We first note that

$$E^* \left( \frac{1}{n} \sum_{i=1}^{n} (w_{i:n} - 1) \right)^2 = E^* \left( \frac{\tau_n}{n} \sum_{i=1}^{n} W_i \right)^2$$
$$= \frac{\tau_n^2}{n^2} \sum_{i=1}^{n} E^* (W_i^2) + \frac{\tau_n^2}{n^2} \sum_{i \neq i_2} E^* (W_{i_1} W_{i_2})$$
$$= \frac{\tau_n^2}{n} + \frac{\tau_n^2}{n^2} n(n - 1) O \left( \frac{1}{n} \right) \to 0, \quad \text{as} \quad n \to \infty.$$

To conclude that, $\frac{1}{n} \sum_{i=1}^{n} w_i - 1 \to^n 0$, as $n \to \infty$. As for the second assertion, we note that since

$$\frac{1}{n} \sum_{i=1}^{n} u_i w_{i:n} = \frac{\tau_n}{n} \sum_{i=1}^{n} u_i W_i + \frac{1}{n} \sum_{i=1}^{n} u_i,$$

and since $\sum_{i=1}^{n} u_i/n \to 0$, as $n \to \infty$, we may only consider the first term. To that end, we note that

$$E^* \left( \frac{\tau_n}{n} \sum_{i=1}^{n} u_i W_i \right)^2 = \frac{\tau_n^2}{n^2} \sum_{i=1}^{n} E^* (u_i^2 W_i^2) + \frac{\tau_n^2}{n^2} \sum_{i \neq i_2} E^* (W_{i_1} W_{i_2} W_{i_1} W_{i_2})$$
$$\leq \left[ 1 + (n - 1) O \left( \frac{1}{n} \right) \right] \frac{\tau_n^2}{n^2} \sum_{i=1}^{n} u_i^2 \to 0,$$

as $n \to \infty$. We therefore conclude that $\frac{1}{n} \sum_{i=1}^{n} u_i w_{i:n} \to^n 0$, as required. □

Lemma 7 Under the conditions of Assumptions A and B, we have that $a_{ni}^{-2} \sum_{j=1}^{n} \phi_{ij}(\hat{\theta}_{ni}) \to^n 1$, for all $i = 1, 2, \ldots, N$.

Proof of Lemma 7: Since $\hat{\theta}_{ni} \to^n \theta_0$, we have

\[ \hat{\theta}_{ni} \to^n \theta_0 \]
\[
\begin{align*}
\alpha_n^{-2} \sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni}) &= \alpha_n^{-2} \sum_{j=1}^{n_i} (y_{ij} - f_{ij}(\hat{\theta}_{ni}))^2 f_{ij}^2(\hat{\theta}_{ni}) \\
&= \alpha_n^{-2} \sum_{j=1}^{n_i} \epsilon_{ij}^2 f_{ij}^2(\hat{\theta}_{ni}) + \alpha_n^{-2} \sum_{j=1}^{n_i} (f_{ij}(\theta_0 + b_i) - f_{ij}(\hat{\theta}_{ni}))^2 f_{ij}^2(\hat{\theta}_{ni}) \\
&+ 2\alpha_n^{-2} \sum_{j=1}^{n_i} \epsilon_{ij}(f_{ij}(\theta_0 + b_i) - f_{ij}(\hat{\theta}_{ni})) f_{ij}^2(\hat{\theta}_{ni}) \\
&\equiv B_1 + B_2 + B_3.
\end{align*}
\]

Write,
\[
B_1 = \alpha_n^{-2} \sum_{j=1}^{n_i} (\epsilon_{ij}^2 - \sigma^2) f_{ij}^2(\hat{\theta}_{ni}) + \alpha_n^{-2} \sigma^2 \sum_{j=1}^{n_i} f_{ij}^2(\hat{\theta}_{ni}).
\]

The first term in \(B_1\) converges to 0 by Assumption A (3), and Corollary A of Wu (1981) while the second term in \(B_1\) converges to 1 by Assumption A(3). Hence \(B_1 \xrightarrow{p} 1\). As for the second and third terms, \(B_2\) and \(B_3\), it follows by a direct application of the Cauchy-Schwarz inequality together with Assumption B (1), that \(B_2 \xrightarrow{p} 0\) and \(B_3 \xrightarrow{p} 0\). Accordingly, it follows that \(\alpha_n^{-2} \sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni}) \xrightarrow{p} 1\), as required.

**Lemma 8** Under the conditions of Assumptions A and B, for all \(i\),
\[
E^*[\tau_n, \alpha_n^{-2} \sup_{|t| \leq K \tau_n} \sum_{j=1}^{n_i} W_{ij} \phi_{1ij}(b_{1i}^*)]^2 \rightarrow 0
\]
where \(b_{1i}^* = \hat{\theta}_{ni} + c \alpha_n^{-1} t\) for some \(0 < c < 1\), as \(n_i \rightarrow \infty\).

**Proof of Lemma 8** We first note that since by Theorem 1, we have \(\hat{\theta}_{ni} - b_i - \theta_0 \xrightarrow{p} 0\), and since
\[
|b_{1i}^* - b_i - \theta_0| = |\hat{\theta}_{ni} - b_i - \theta_0 + c \alpha_n^{-1} t| \\
\leq |\hat{\theta}_{ni} - b_i - \theta_0| + \frac{c \tau_n \sqrt{n_i} |t|}{\alpha_n \tau_n},
\]
it follows under Assumption B (3) that with \(|t| \leq K \tau_n\), we have \(b_{1i}^* - b_i - \theta_0 \xrightarrow{p} 0\). Thus,
In light of Assumption B (2–3), and that \( s_{ni}^2 = \gamma (b_{ni}^*) \leq \kappa \), we only need to show, in order to complete the proof of Lemma 8, that

\[
\lim_{n_i \to \infty} \frac{1}{n_i} \sum_{|i| \leq K} \phi_{ij}^2(b_{ni}^*) < \infty.
\]

Toward that end, we note that,

\[
E_n^* \left[ a_n^{-2} \sup_{|i| \leq K} \sum_{j=1}^{n_i} W_{ij} \phi_{ij}(b_{ni}^*) \right]^2
\]

\[
\leq \tau_n^2 a_n^{-4} \sup_{|i| \leq K} \left[ \sum_{j=1}^{n_i} \phi_{ij}^2(b_{ni}^*) + O(\frac{1}{n_i}) \sum_{j \neq j_1}^{n_i} \phi_{iij_1}(b_{ni}^*) \phi_{iij_2}(b_{ni}^*) \right]
\]

\[
\leq \tau_n^2 a_n^{-4} \sup_{|i| \leq K} \left[ \sum_{j=1}^{n_i} \phi_{ij}^2(b_{ni}^*) + O(\frac{1}{n_i}) (n_i - 1) \sum_{j=1}^{n_i} \phi_{ij}^2(b_{ni}^*) \right]
\]

\[
= \tau_n^2 a_n^{-4} \left[ O(\frac{1}{n_i}) (n_i - 1) + 1 \right] \sup_{|i| \leq K} \sum_{j=1}^{n_i} \phi_{ij}^2(b_{ni}^*).
\]

It is straightforward to see that by Assumption B (1), \( \lim_{n_i \to \infty} I_1 < \infty \), and that by Cauchy-Schwarz inequality \( \lim_{n_i \to \infty} I_3 < \infty \). Finally we write
\[ I_2 = a_{n_i}^{-2} \sup_{|i| \leq K \tau_{n_i}} \sum_{j=1}^{n_i} (e_{ij}^2 - \sigma^2 f_{ij}''(b_{11}^*)) + a_{n_i}^{-2} \sup_{|i| \leq K \tau_{n_i}} \sum_{j=1}^{n_i} \sigma^2 f_{ij}''(b_{11}^*) \]
\[ + a_{n_i}^{-2} \sup_{|i| \leq K \tau_{n_i}} \sum_{j=1}^{n_i} (f_{ij}(\theta_0 + b_i) - f_{ij}(b_{11}^*))^2 f_{ij}''(b_{11}^*) \]
\[ + 2a_{n_i}^{-2} \sup_{|i| \leq K \tau_{n_i}} \left| \sum_{j=1}^{n_i} \epsilon_{ij}(f_{ij}(\theta_0 + b_i) - f_{ij}(b_{11}^*)) f_{ij}''(b_{11}^*) \right|. \]

The first term converges to 0 in probability by Assumption B (2) and Corollary A of Wu (1981). Then, according to Assumption A (2),
\[ \lim_{n_i \to \infty} a_{n_i}^{-2} \sup_{|i| \leq K \tau_{n_i}} \sum_{j=1}^{n_i} \sigma^2 f_{ij}''(b_{11}^*) < \infty. \]

The third term in \( I_2 \) converges to 0 in probability by an application of the Cauchy-Schwarz inequality combined with Assumption B (1) and (2). Finally, the fourth term in \( I_2 \), converges to 0 in probability again, by an application of the Cauchy-Schwarz inequality. Thus we have \( \lim_{n_i \to \infty} I_2 < \infty \). Accordingly, we have established that as \( n_i \to \infty \),
\[ E^* \left[ \tau_{n_i} a_{n_i}^{-2} \sup_{|i| \leq K \tau_{n_i}} \sum_{j=1}^{n_i} W_{ij} \phi_{ij}(b_{11}^*) \right]^2 \to 0. \]

**Lemma 9** Under the conditions of Assumptions A and B, there exists a \( K > 0 \) such that for any \( \epsilon > 0 \),
\[ P^* \left[ a_{n_i}^{-1} \sum_{j=1}^{n_i} W_{ij} \phi_{ij}(\hat{\theta}_{ni}) > K \right] < \frac{\epsilon}{2}. \]

**Proof of Lemma 9** By Lemma 7.
Further, we have

\[ V^*(a_n^{-1} \sum_{j=1}^{n_i} W_{ij} \phi_{ij}(\hat{\theta}_{ni})) \]

\[ = a_n^{-2} \sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni}) + a_n^{-2} O\left(\frac{1}{n_i} \sum_{j \neq j_2} \phi_{ij}(\hat{\theta}_{ni}) \phi_{ij_2}(\hat{\theta}_{ni})\right) \]

\[ = a_n^{-2} \sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni}) + a_n^{-2} O\left(\frac{1}{n_i} \sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni})\right) - a_n^{-2} O\left(\frac{1}{n_i} \sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni})\right) \]

\[ \leq a_n^{-2} (1 - O\left(\frac{1}{n_i}\right)) \sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni}) \xrightarrow{p} 1. \]

Hence we obtain,

\[ P^*(\left| a_n^{-1} \sum_{j=1}^{n_i} W_{ij} \phi_{ij}(\hat{\theta}_{ni}) \right| > K) \leq \frac{V^*(a_n^{-1} \sum_{j=1}^{n_i} W_{ij} \phi_{ij}(\hat{\theta}_{ni}))}{K^2} \xrightarrow{p} \frac{1}{K^2}. \]

Accordingly, there exists a \( K > 0 \) such that for any \( \epsilon > 0 \),

\[ P^* \left[ a_n^{-1} \sum_{j=1}^{n_i} W_{ij} \phi_{ij}(\hat{\theta}_{ni}) > K \right] < \frac{\epsilon}{2}. \]

\[ \square \]

**Proof of Theorem 3** Let

\[ S_{n_i}^*(t) := a_n^{-1} \sum_{j=1}^{n_i} w_{ij} \left[ \phi_{ij}(\hat{\theta}_{ni} + a_n^{-1} t) - \phi_{ij}(\hat{\theta}_{ni}) \right] - \frac{t}{\sigma^2}. \]  

(19)

First, we will show that for any given \( K > 0 \),

\[ E^* \left[ \tau_{n_i}^{-1} \sup_{|t| \leq K \tau_{n_i}} \left| S_{n_i}^*(t) \right| \right] \xrightarrow{p} 0. \]  

(20)

By a Taylor expansion we have that \( \phi_{ij}(\hat{\theta}_{ni} + a_n^{-1} t) = \phi_{ij}(\hat{\theta}_{ni}) + \phi_{1ij}(b_{i1}^*) a_n^{-1} t \), where as before, \( b_{i1}^* = \hat{\theta}_{ni} + c a_n^{-1} t \) for some \( 0 < c < 1 \). Accordingly we obtain,

\[ \tau_{n_i}^{-1} \sup_{|t| \leq K \tau_{n_i}} \left| S_{n_i}^*(t) \right| = \tau_{n_i}^{-1} \sup_{|t| \leq K \tau_{n_i}} \left| a_n^{-1} \sum_{j=1}^{n_i} w_{ij} \phi_{1ij}(b_{i1}^*) a_n^{-1} t - \frac{t}{\sigma^2} \right| \]

\[ = K \left| a_n^{-2} \sup_{|t| \leq K \tau_{n_i}} \sum_{j=1}^{n_i} w_{ij} \phi_{1ij}(b_{i1}^*) - \frac{1}{\sigma^2} \right| \]

\[ \leq K \tau_{n_i} a_n^{-2} \sup_{|t| \leq K \tau_{n_i}} \left| \sum_{j=1}^{n_i} w_{ij} \phi_{1ij}(b_{i1}^*) \right| + K \left| a_n^{-2} \sup_{|t| \leq K \tau_{n_i}} \sum_{j=1}^{n_i} \phi_{1ij}(b_{i1}^*) - \frac{1}{\sigma^2} \right|. \]

Further,
By Lemma 8 and Lemma 1, we have

$$E^* \left[ \tau_n^{-1} \sup_{|t| \leq K \tau_n} |S_n^w(t)| \right] ^2 \leq K^2 E^* \left[ \tau_n a_n^{-2} \sup_{|t| \leq K \tau_n} \sum_{j=1}^{n_i} W_{ij} \phi_{1ij} (b_{1i}^*) \right] ^2$$

$$+ K^2 E^* \left[ a_n^{-2} \sup_{|t| \leq K \tau_n} \sum_{j=1}^{n_i} \phi_{1ij} (b_{1i}^*) - \frac{1}{\sigma^2} \right] ^2$$

$$+ K^2 E^* \left[ \tau_n a_n^{-2} \sup_{|t| \leq K \tau_n} \sum_{j=1}^{n_i} W_{ij} \phi_{1ij} (b_{1i}^*) \right] \left[ a_n^{-2} \sup_{|t| \leq K \tau_n} \sum_{j=1}^{n_i} \phi_{1ij} (b_{1i}^*) - \frac{1}{\sigma^2} \right] .$$

Thus, by an application of the Cauchy-Schwarz inequality we have proved (20).

Next, in light of (19) we define

$$A_n^w (t) := a_n^{-1} t \sum_{j=1}^{n_i} w_{ij} \phi_{ij} (\hat{\theta}_{ni} + a_n^{-1} t) = t S_n^w (t) + a_n^{-1} t \sum_{j=1}^{n_i} w_{ij} \phi_{ij} (\hat{\theta}_{ni}) + \frac{t^2}{\sigma^2}.$$ 

Accordingly,

$$\inf_{|t| = K \tau_n} A_n^w (t) \geq - K \tau_n \sup_{|t| = K \tau_n} |S_n^w (t)| - K \tau_n a_n^{-1} \sum_{j=1}^{n_i} w_{ij} \phi_{ij} (\hat{\theta}_{ni}) + \frac{K^2 \tau_n^2}{\sigma^2}.$$ 

Recall that by Lemma 9, there exists a $K > 0$ such that for any $\epsilon > 0$,

$$P^* \left[ a_n^{-1} \sum_{j=1}^{n_i} W_{ij} \phi_{ij} (\hat{\theta}_{ni}) > K \right] < \frac{\epsilon}{2}.$$ 

Accordingly, by (21) and (20) we may choose large enough $K$ such that for sufficiently large $n_i$, 

$$\inf_{|t| = K \tau_n} A_n^w (t) \geq - K \tau_n \sup_{|t| = K \tau_n} |S_n^w (t)|.$$ 

Thus, by an application of the Cauchy-Schwarz inequality we have proved (20).
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\[ P^* \left( \inf_{|t| = K\tau_n} A_n(t) \geq 0 \right) \geq P^* \left( \sup_{|t| = K\tau_n} |S_n^*(t)| + a_n^{-1} \sum_{j=1}^n w_{ij} \phi_j(\hat{\theta}_n) \right) \leq \frac{K\tau_n}{\sigma^2} \]

\[ = P^* \left( \sup_{|t| = K\tau_n} |S_n^*(t)| + a_n^{-1} \sum_{j=1}^n W_{ij} \phi_j(\hat{\theta}_n) \right) \leq \frac{K\tau_n}{\sigma^2} \]

\[ = 1 - P^* \left( \sup_{|t| = K\tau_n} |S_n^*(t)| + a_n^{-1} \sum_{j=1}^n W_{ij} \phi_j(\hat{\theta}_n) > \frac{K\tau_n}{\sigma^2} \right) \]

\[ \geq 1 - P^* \left[ \tau_{-1} \sup_{|t| = K\tau_n} |S_n^*(t)| > \frac{K}{4\sigma^2} \right] - P^* \left[ a_n^{-1} \sum_{j=1}^n W_{ij} \phi_j(\hat{\theta}_n) > \frac{K}{4\sigma^2} \right] \]

\[ \geq 1 - \epsilon. \]

From the continuity of \( \sum_{j=1}^n \phi_j(\theta) \) in \( \theta \), we have for sufficiently large \( n_i \), that there exists a \( K \) such that the equation \( \sum_{j=1}^n w_{ij} \phi_j(\hat{\theta}_n) + a_n^{-1} t = 0 \), has a root, \( t = T_{ni} \), with a probability larger than \( 1 - \epsilon \). That is, we have \( \hat{\theta}_{ni} = \hat{\theta}_n + a_n^{-1} T_{ni} \), where \( |\tau_{-1}^{-1} T_{ni}| < K \) in probability. Accordingly we may rewrite \( \hat{\theta}_{\text{RTS}} \) as,

\[ \hat{\theta}_{\text{RTS}} = \frac{1}{N} \sum_{i=1}^N u_i \hat{\theta}_n + \frac{1}{N} \sum_{i=1}^N u_i a_n^{-1} T_{ni} \]

\[ = \frac{1}{N} \sum_{i=1}^N u_i (\theta_0 + b_i + a_n^{-1} T_{ni}) + \frac{1}{N} \sum_{i=1}^N u_i a_n^{-1} T_{ni} \]

\[ = \frac{1}{N} \sum_{i=1}^N u_i \theta_0 + \frac{1}{N} \sum_{i=1}^N u_i b_i + \frac{1}{N} \sum_{i=1}^N u_i a_n^{-1} T_{ni} + \frac{1}{N} \sum_{i=1}^N u_i a_n^{-1} T_{ni}. \]

That is,

\[ \theta_{\text{RTS}}^* - \theta_0 = \frac{1}{N} \sum_{i=1}^N (u_i - 1) \theta_0 + \frac{1}{N} \sum_{i=1}^N u_i b_i + \frac{1}{N} \sum_{i=1}^N u_i a_n^{-1} T_{ni} + \frac{1}{N} \sum_{i=1}^N u_i a_n^{-1} T_{ni}. \]

Additionally, by Lemma 6, we have \( \frac{1}{N} \sum_{i=1}^N (u_i - 1) \rightarrow P^* \) as well as, \( \frac{1}{N} \sum_{i=1}^N u_i b_i \rightarrow 0 \). Further, we also have that

\[ \frac{1}{N} \sum_{i=1}^N u_i a_n^{-1} T_{ni} = \frac{1}{N} \sum_{i=1}^N (u_i - 1) a_n^{-1} T_{ni} + \frac{1}{N} \sum_{i=1}^N a_n^{-1} T_{ni}. \]

Now by Lemma 2 and the fact \( T_{ni} = O_p(1) \), we obtain, with \( U_i := (u_i - 1)/\tau_N \), that
\[ E^* \left( \frac{1}{N} \sum_{i=1}^{N} (u_i - 1)a_{ni}^{-1} T_{ni} \right)^2 = E^* \left( \frac{\tau_N}{N} \sum_{i=1}^{N} U_i a_{ni}^{-1} T_{ni} \right)^2 \]

\[ \leq \frac{\tau_N^2}{N^2} \sum_{i=1}^{N} a_{ni}^{-2} T_{ni}^2 + (N - 1) O \left( \frac{1}{N} \right) \frac{\tau_N^2}{N^2} \sum_{i=1}^{N} a_{ni}^{-2} T_{ni}^2 \xrightarrow{p} 0, \]

as well as, \[ \frac{1}{N} \sum_{i=1}^{N} a_{ni}^{-1} T_{ni} \xrightarrow{p} 0. \] That is, we have established that, \[ E^* \left( \frac{1}{N} \sum_{i=1}^{N} u_i a_{ni}^{-1} T_{ni} \right)^2 \xrightarrow{p} 0. \] Accordingly we conclude, \[ P^* \left( \left| \frac{1}{N} \sum_{i=1}^{N} u_i a_{ni}^{-1} T_{ni} \right| > \epsilon \right) = o_p(1). \] Similarly,

\[ \frac{1}{N} \sum_{i=1}^{N} u_i a_{ni}^{-1} T_{ni}^* = \frac{1}{N} \sum_{i=1}^{N} (u_i - 1) a_{ni}^{-1} T_{ni}^* + \frac{1}{N} \sum_{i=1}^{N} a_{ni}^{-1} T_{ni}^*, \]

where by Lemma 2, Assumption B (3) and the fact \( \tau_{ni}^{-1} T_{ni}^* = O_p(1) \), we obtain,

\[ E^* \left( \frac{1}{N} \sum_{i=1}^{N} (u_i - 1) a_{ni}^{-1} T_{ni}^* \right)^2 = E^* \left( \frac{\tau_N}{N} \sum_{i=1}^{N} U_i a_{ni}^{-1} T_{ni}^* \right)^2 \]

\[ \leq \frac{\tau_N^2}{N^2} \sum_{i=1}^{N} a_{ni}^{-2} T_{ni}^* + (N - 1) O \left( \frac{1}{N} \right) \frac{\tau_N^2}{N^2} \sum_{i=1}^{N} a_{ni}^{-2} T_{ni}^* \]

\[ = (1 + (N - 1) O \left( \frac{1}{N} \right)) \frac{\tau_N^2}{N^2} \sum_{i=1}^{N} \frac{\tau_{ni}^2}{a_{ni}} \frac{1}{a_{ni}} T_{ni}^* \xrightarrow{p} 0. \]

Finally, by Lemma 2,

\[ \frac{1}{N} \sum_{i=1}^{N} a_{ni}^{-1} T_{ni}^* = \frac{1}{N} \sum_{i=1}^{N} \frac{\tau_{ni}}{a_{ni}} \tau_{ni}^{-1} T_{ni}^* \xrightarrow{p} 0. \]

Accordingly we also conclude that, \( P^* \left( \left| \frac{1}{N} \sum_{i=1}^{N} u_i a_{ni}^{-1} T_{ni}^* \right| > \epsilon \right) = o_p(1). \) Hence, we have proved that \( P^* \left( \left| \hat{\theta}_{RTS}^* - \theta_0 \right| > \epsilon \right) = o_p(1). \)

For the related asymptotic normality results as stated in Theorem 4, we need the following two Lemmas.

**Lemma 10** Suppose that the conditions of Assumptions A and B hold. If \( \frac{\tau_n}{\tau_N} = o \left( \sqrt{n_i} \right) \) then as \( n_i \to \infty \) and \( N \to \infty \),

\[ \frac{\tau_{ni}^{-1}}{\sqrt{N}} \sum_{i=1}^{n_i} u_i a_{ni}^{-2} \sum_{j=1}^{n_i} w_{ij} \phi_{ij} (\hat{\theta}_{ni}) \xrightarrow{p} 0. \]

**Proof of Lemma 10** Let

\[ \hat{\theta}_{RTS}^* - \theta_0 \xrightarrow{d} N(0, \Sigma), \]

where

\[ \Sigma_{ij} = \frac{\tau_{ni}^{-1}}{\sqrt{N}} \sum_{i=1}^{n_i} a_{ni}^{-1} \sum_{j=1}^{n_i} w_{ij} \phi_{ij} (\hat{\theta}_{ni}). \]

The proof follows by applying the Delta Method.

\[ \hat{\theta}_{RTS}^* \xrightarrow{d} N(\theta_0, \Sigma). \]

\[ \hat{\theta}_{RTS}^* - \theta_0 \xrightarrow{d} N(0, \Sigma). \]

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Clearly $E^*(X_{ni}^*) = 0$, and $X_{ni}^*$ are independent for $i$ in $1,2,\ldots,N$. Further, by Lemma 7 we have, as $n_i \to \infty$, that

$$E^*(X_{ni}^2) = E^*(a_n^{-1}\sum_{j=1}^{n_i} W_{ij} \phi_{ij}(\hat{\theta}_{ni}))^2$$

$$= a_n^{-2}\sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni}) + O(\frac{1}{n_i})\sum_{j_1 \neq j_2} \phi_{ij_1}(\hat{\theta}_{ni}) \phi_{ij_2}(\hat{\theta}_{ni})$$

$$= a_n^{-2}\sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni}) + O(\frac{1}{n_i})\left(\sum_{j=1}^{n_i} \phi_{ij}(\hat{\theta}_{ni})\right)^2 - O(\frac{1}{n_i})\sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni})$$

$$= (1 - O(\frac{1}{n_i}))a_n^{-2}\sum_{j=1}^{n_i} \phi_{ij}^2(\hat{\theta}_{ni}) \to 1.$$  

Thus, with $U_i = (u_i - 1)/\sqrt{\tau_N}$,

$$\frac{\tau_N^{-1}}{\sqrt{N}} \sum_{i=1}^{N} U_i a_n^{-2}\sum_{j=1}^{n_i} W_{ij} \phi_{ij}(\hat{\theta}_{ni}) = \frac{\tau_N^{-1}}{\sqrt{N}} \sum_{i=1}^{N} u_i a_n^{-1} \tau_n X_{ni}^*$$

$$= \frac{1}{\sqrt{N}} \sum_{i=1}^{N} U_i a_n^{-1} \tau_n X_{ni}^* + \frac{\tau_N^{-1}}{\sqrt{N}} \sum_{i=1}^{N} a_n^{-1} \tau_n X_{ni}^*.$$  

Since $U_i$ and $X_{ni}^*$ are independent, we obtain,

$$E^*(\frac{1}{\sqrt{N}} \sum_{i=1}^{N} U_i a_n^{-1} \tau_n X_{ni}^*)^2 = \frac{1}{N} \sum_{i=1}^{N} E^*(U_i^2 a_n^{-2} \tau_n^2 X_{ni}^{*2})$$

$$+ \sum_{i_1 \neq i_2} E^*(U_{i_1}U_{i_2} a_n^{-1} a_n^{-1} \tau_n \tau_n X_{ni_1}^* X_{ni_2}^*)$$

$$= \frac{1}{N} \sum_{i=1}^{N} a_n^{-2} \tau_n^2 E^*(X_{ni}^{*2}) \to 0.$$  

Finally, since $\frac{\tau_n}{\tau_N} = o(\sqrt{n_i})$, we also have,

$$E^*(\frac{\tau_N^{-1}}{\sqrt{N}} \sum_{i=1}^{N} a_n^{-1} \tau_n X_{ni}^*)^2 = \frac{\tau_N^{-2}}{N} \sum_{i=1}^{N} a_n^{-2} \tau_n^2 E^*(X_{ni}^{*2})$$

$$= \frac{1}{N} \sum_{i=1}^{N} a_n^{-2} \tau_n^2 E^*(X_{ni}^{*2}) \to 0.$$  

Accordingly we obtain that,
Lemma 11 Suppose that the conditions of Assumptions A and B hold. If \( \frac{\tau_n}{\sqrt{N}} = o(\sqrt{n_i}) \) then as \( n_i \to \infty \) and \( N \to \infty \),

\[
\frac{\lambda^{-1} \tau_N^{-1} \sigma^2}{\sqrt{N}} \sum_{i=1}^{N} u_i a_{n_i}^{-1} \sum_{j=1}^{n_i} w_{ij} \phi_{ij}(\hat{\theta}_{ni}) \overset{p}{\to} 0.
\]

Proof of Lemma 11 We first write

\[
\frac{\lambda^{-1} \tau_N^{-1} \sigma^2}{\sqrt{N}} \sum_{i=1}^{N} u_i a_{n_i}^{-1} S_n(T^*_ni) \overset{p}{\to} 0.
\]

By Lemma 2, Assumption B (3) and the fact \( \tau_N^{-1} S_n(T^*_ni) \overset{p}{\to} 0 \),

\[
\frac{\lambda^{-1} \tau_N^{-1} \sigma^2}{\sqrt{N}} \sum_{i=1}^{N} a_{n_i}^{-1} S_n(T^*_ni) \overset{p}{\to} 0.
\]

Further, it can be seen that,

\[
E^*(\frac{1}{\sqrt{N}} \sum_{i=1}^{N} U_i a_{n_i}^{-1} S_n(T^*_ni))^2 \leq \frac{1}{N} \left[ 1 + (N - 1)O(\frac{1}{N}) \right] \sum_{i=1}^{N} a_{n_i}^{-2} E^*(S^2_n(T^*_ni)) \to 0.
\]

Thus we have,

\[
\frac{\lambda^{-1} \tau_N^{-1} \sigma^2}{\sqrt{N}} \sum_{i=1}^{N} u_i a_{n_i}^{-1} S_n(T^*_ni) \overset{p}{\to} 0.
\]

We conclude the “Appendix” with a proof of Theorem 4.

Proof of Theorem 4 By Theorem 3 and (19) we express,

\[
\hat{\theta}^+_ni - \hat{\theta}^-ni = -a_{n_i}^{-2} \sigma^2 \sum_{j=1}^{n_i} w_{ij} \phi_{ij}(\hat{\theta}_{ni}) - a_{n_i}^{-1} \sigma^2 S_n(T^*_ni).
\]

Accordingly we have,
\[ \hat{\theta}^*_{SRS} - \hat{\theta}_{STS} = \frac{1}{N} \sum_{i=1}^{N} (u_i - 1) \hat{\theta}_{ni} - \frac{\sigma^2}{N} \sum_{i=1}^{N} u_i a_{ni}^{-2} \sum_{j=1}^{n_i} w_{ij} \phi_{ij}(\hat{\theta}_{ni}) - \frac{\sigma^2}{N} \sum_{i=1}^{N} u_i a_{ni}^{-1} S_n(T^*_n), \]

where \(|T^*_n| < K \tau_n\) in probability. Further,

\[ \lambda^{-1} \tau_{N}^{-1} \sqrt{N}(\hat{\theta}^*_{SRS} - \hat{\theta}_{STS}) = \lambda^{-1} \tau_{N}^{-1} \sqrt{N} \sum_{i=1}^{N} (u_i - 1) \hat{\theta}_{ni} \]

\[ - \frac{\lambda^{-1} \tau_{N}^{-1} \sigma^2}{\sqrt{N}} \sum_{i=1}^{N} u_i a_{ni}^{-2} \sum_{j=1}^{n_i} w_{ij} \phi_{ij}(\hat{\theta}_{ni}) \]

\[ - \frac{\lambda^{-1} \tau_{N}^{-1} \sigma^2}{\sqrt{N}} \sum_{i=1}^{N} u_i a_{ni}^{-1} S_n(T^*_n), \]

\[ \equiv I_1 + I_2 + I_3. \]

By Lemma 10, \(I_2 \overset{p^*}{\to} 0\), and by Lemma 11, \(I_3 \overset{p^*}{\to} 0\), and therefore it remains only to consider \(I_1\). Now, observe that,

\[ I_1 := \lambda^{-1} \tau_{N}^{-1} \sqrt{N} \sum_{i=1}^{N} (u_i - 1) \hat{\theta}_{ni} = \lambda^{-1} \tau_{N}^{-1} \sqrt{N} \sum_{i=1}^{N} U_i (b_i + \theta_0) + \lambda^{-1} \tau_{N}^{-1} \sum_{i=1}^{N} U_i a_{ni}^{-1} T_{ni}. \]

By Lemma 2,

\[ E^* \left( \frac{1}{\sqrt{N}} \sum_{i=1}^{N} U_i a_{ni}^{-1} T_{ni} \right)^2 \leq \frac{1}{N} \sum_{i=1}^{N} a_{ni}^{-2} S_{ni}^2 + (N - 1) O\left( \frac{1}{N} \right) \sum_{i=1}^{N} a_{ni}^{-2} S_{ni}^2 \overset{p^*}{\to} 0. \]

Further by Lemma 5,

\[ \bar{U}_N := \frac{1}{N} \sum_{i=1}^{N} U_i = \frac{1}{N} \sum_{i=1}^{N} \frac{u_i - 1}{\lambda_{N}^{-1}} \overset{p^*}{\to} 0, \]

and clearly, \(\sqrt{N}(\bar{b} + \theta_0) \Rightarrow \mathcal{N}(\theta_0, \lambda^2)\). Accordingly we have, \(\frac{\lambda^{-1} \tau_{N}^{-1} \sum_{i=1}^{N} (b_i - b)^2}{N} \overset{a.s.}{\to} 1\) as well as \(\sqrt{N} \bar{U}(\bar{b} + \theta_0) \overset{p^*}{\to} 0\). Further, by Lemma 4.6 of Praestgaard and Wellner (1993), we have that

\[ \frac{\lambda^{-1} \tau_{N}^{-1} \sum_{i=1}^{N} U_i (b_i + \theta_0)}{\sqrt{N}} \Rightarrow \mathcal{N}(0, 1). \]

Thus we have

\[ \frac{\lambda^{-1} \tau_{N}^{-1} \sum_{i=1}^{N} (u_i - 1) \hat{\theta}_{ni}}{\sqrt{N}} \Rightarrow \mathcal{N}(0, 1). \]

Finally we conclude that as \(n_i \to \infty\) and \(N \to \infty\),
\[ \lambda^{-1} \tau_N^{-1} \sqrt{N(\hat{\theta}_{RTS} - \hat{\theta}_{STS})} \Rightarrow \mathcal{N}(0, 1). \]

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Availability of data and material Derived data supporting the findings of this study are available as Theoph under the R package.

Declarations

Conflict of interest No conflicts of interest.

Code availability The code supporting this study are available from the corresponding author upon reasonable request.

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