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Exploring Optimal Design of Experiments for Random Effects Models

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EXPLORING OPTIMAL DESIGN OF EXPERIMENTS FOR RANDOM EFFECTS MODELS

by

Ryan C. Bushman

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ABSTRACT

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by

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Utah State University, 2024

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The majority of research in the field of optimal design of experiments has focused on a fixed effects model. The purpose of this thesis is to explore how the optimal design framework applies to a nested random effects model. Given the covariance matrix of the maximum likelihood estimators for a model is the inverse of the model's information matrix, the optimal design framework operates by simultaneously maximizing the information obtained in an experiment and minimizing the variance of the model's maximum likelihood estimators. Unlike the typical fixed effects experiment, the optimization of the information matrix for a random effects model is non-linear as the information matrix is a function of the experiment's sample sizes and the values—often hypothesized—of the true variance components. The calculation of the information matrix for a random effects experiment is much more difficult than for a fixed effects experiment. Very little research has been done in this field by a few researchers from several decades ago; some of this research exists in only a single print copy. To the best of our knowledge, tools do not exist that leverage this research for the common statistical coding languages used today. The purpose of this thesis is to revive the research that has been done in this field and build a free open-source R package, ODVC (Optimal Design for Variance Components), that enables users to do optimal design of experiments for one-way and two-

way random effects models. To demonstrate the use of the ODVC package, we explore interesting problems in both the one-way and two-way nested experiment settings.

(73 pages)

PUBLIC ABSTRACT

Exploring Optimal Design of Experiments for Random Effects Models

Ryan C. Bushman

The majority of research in the field of optimal design of experiments has focused on producing designs for fixed effects models. The purpose of this thesis is to explore how the optimal design framework applies to nested random effects models. The object that is being optimized is the model information matrix. We explore the full derivation of the random effects information matrix to highlight the complexity of the problem and show how the optimization is a function of the model's parameters. In conjunction with this research, the ODVC (Optimal Design for Variance Components) package was built to provide tools that allow researchers to explore interesting optimal design problems for both one-way and two-way nested random effects models. The tools within this package were used to explore how the choice of an optimal design for a random effects model is influenced by the values of the hypothesized variance components, the sample sizes, and the choice of optimality criteria.

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Ryan C. Bushman

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INTRODUCTION AND LITERATURE REVIEW

1.1
Introduction

In 2018, an article by Willis Jensen outlined six open problems in the field of optimal design of experiments. One of the problems he outlined was optimal design for the estimation of variance components—i.e., random effects models. The majority of professionals that practice optimal design of experiments focus primarily on fixed effects models. Those who do academic research in optimal design of experiments often focus on algorithm development and generating new designs. For several examples, see [1, 2, 3, 4, 5].

However, in industry there are many situations in which an experiment may be conducted to determine how random effects influence a process or procedure [6]. Estimating variances as an uncertainty quantification tool is commonly applied in metrological and analytical (e.g., chemistry) settings. See [7, 8] for two examples where estimated variances are used to support development and validation of analytical methods. An example of improving estimation of a single population variance by a small number of replicates is provided in [8]. A detailed example of a two-staged nested random-effects ANOVA used as an experimental design to conduct a material heterogeneity study can be found in [9]. Accredited analytical laboratories are required to follow the international standard guidelines for conducting material heterogeneity studies under variance component designs. In these settings, the default procedure is often to use a balanced design [10].

If one will conduct the F-tests for whether a specific variance component is 0, then there are compelling arguments for implementing balanced multi-stage nested variance component designs, see [11]. If the variance component design is unbalanced, the typical F-tests may only be approximate or completely broken by specific data [11] and it can be difficult to determine when the F-tests can be trusted. However, chemical metrologists typically don't need these significance tests, but only require the variance estimates to be used in a larger uncertainty quantification calculation. In

this case, there is a compelling argument to implement a non-balanced design as a balanced design will inflate the degrees-of-freedom to a large number for the residual error variance. The residual error variance is typically already well known as it usually represents the short-term measurement repeatability in such experiments. Therefore, it would be better to use the optimal design framework to ensure the precise estimation of each variance component. The purpose of this work is to build a set of tools that allows practitioners to explore candidate optimal experiment designs for nested one-way and two-way variance component models. Mixed effects models fall outside of the scope of this research, but are an area of future research under consideration.

1.2

Background

There are many reasons why the literature for such problems is scarce. Optimal design of experiments uses the information matrix of the model in question as the object to be optimized. In the standard case in which the model only has fixed effects, the information matrix is easily derived. When working with models that only have random effects, the calculation for the information matrix is not as commonly known and more complex. Using maximum likelihood estimation theory, we know that the information matrix is the Hessian of negative log-likelihood function of our model [12]. The computation of the Hessian for a model that only contains random effects is very difficult as it requires the use of many uncommon matrix derivative identities (e.g., the derivative of the log determinant of a matrix with respect to a scalar) and strategic use of the trace function to simplify the end result. An additional barrier to conducting research in this area is that for a model that only contains random effects, the information matrix will be a function of the sample sizes and the values of the variance components — the parameters — which results in a non-linear optimization problem. Given the variance components are often unknown prior to an experiment, hypothesized values for these parameters must be used instead in order to explore quality of differing candidate designs. Intuition may also lead one to incorrectly assume that if the information matrix is a function of the sample sizes, the optimal design is simply the one with the largest number of experimental runs. Given these barriers, there has been little research conducted on optimal design for random effects models. However, there is a need for research in this area of optimal design of experiments. Any profession that relies on uncertainty quantification, such as chemists, benefits from nested random effects experiments. Given these experiments can be expensive, the optimal design framework is useful as it focuses on maximizing information and minimizing variance for the fixed number of

experimental runs that are deemed affordable.

1.3

Literature Review

One of the foremost researchers on the subject of variance component models is Dr. Shayle R. Searle. In 1970 he published an article that focused on using maximum likelihood estimation as a route to calculating large sample variance-covariance matrices for unbalanced data. He begins with an eloquent description of the process: "Estimation of variance components from data that are unbalanced ... has been referred to by Hartley ... as involving 'algebraic heroics.' Obtaining sampling variances can be described similarly." He mentions that approaching this problem from the perspective of maximum likelihood estimation is uncommon because of its inherent complexity [13]. However, using a well-suited vector/matrix notation, he derives a generalized element-wise expression for the Hessian of a nested random effects model. He then goes on to demonstrate its functionality in the one-way and two-way nested model setting. This information is not easily usable for the average practitioner as it requires a strong background in statistics and use of a unique matrix/vector notation.

Searle went on to write a book on the subject of variance components alongside George Casella and Charles McCulloch. In the third Chapter they go through the one-way classification. They revisit the vector/matrix notation that makes working the problem significantly easier. After going through the maximum likelihood estimation, they demonstrate the calculation of the asymptotic covariance matrix for the maximum likelihood estimators for both balanced and unbalanced data [14]. They establish that these asymptotic covariance matrices can also be calculated using the generalized element-wise expression for the Hessian of nested random models published in Searle 1970 [13].

Another example of research done in this area of optimal design of experiments is a Doctoral Dissertation by Dr. Jaime Delgado at Colorado State University (CSU) in 1997. His research, largely inspired by the work of Goldsmith and Gaylor [15], focused on optimal design of experiments for one, two, and three-way nested variance component models. He was particularly interested in finding unbalanced optimal designs that allow for each variance component to be estimated with approximately equal precision. A common problem in nested models is the majority of the degrees of freedom are allocated to the bottom level of an experiment. This allows σ^2 to be estimated with very high precision. However, if the focus of the experiment is to study the effects of a different

variance component, σ_A^2, then it would be desirable to allocate degrees of freedom such that it is estimated with high precision as well. Delgado calculated the information matrix for the models in question by using method of moment estimators. The criteria by which he scored designs were the determinant, trace, and scaled trace criteria. Delgado was preferential to the scaled trace criteria as it emphasized taking into account the values of the variance components when scoring a design [16]. Delgado went on to write a paper with Hari Iyer on optimal designs for three stage nested random models. Similar to his dissertation he explores using the scaled trace criteria. Using a parameterization that emphasizes the ratios of the variance components they are able to conduct numerical optimization and find designs that are more efficient that previously published designs [17].

1.4

Conclusion

A major motivation in conducting research in optimal design of experiments for variance component models is the fact that despite that it would be a useful tool in domains that use variance components models as an uncertainty quantification tool, there are very few researchers who have worked on this problem. Some of the work that was reviewed in this section is only available to the public in the form a single printed copy.

In this thesis, we will add to the literature by showing a complete annotated derivation of the information matrix for nested random effects models. This is an important exercise to truly understand how optimal design for such models fundamentally changes as the object being optimized is a function of the model's parameters. Once we have illustrated this derivation, we will go on to demonstrate how tools within the ODVC package—accessed at `https://github.com/ryancbushman/ODVC`—use the aforementioned information matrix derivation to allow researchers to do optimal design of experiments for nested random effects models. While inspired by those referenced in the literature review, these tools allow one to explore designs of greater size with more complex nesting structures. Additionally, this package has been written in a contemporary statistics coding language and made available on an open-source and free platform. The goal of this work is to build on the knowledge established past researchers and create tools that will allow practitioners to easily find experiment designs that offer optimal or near optimal performance and are tailored to be cost effective according to the restraints put on the practitioner.

CHAPTER 2
DERIVING THE INFORMATION MATRIX FOR THE ONE-WAY ANOVA MODEL

Although the knowledge to derive the information matrix for the one-way ANOVA model exists in the literature, we did not encounter a complete annotated derivation in any one source. This chapter contains a clear and complete explanation of how to derive the information matrix for a random effects model and highlights how the understanding gained from this derivation influences how one would do optimal design of experiments for such models. The final result of this derivation can be found in reference [13].

When attempting to conduct optimal design of experiments for models that only have random effects, the simplest version of this problem uses the one-way ANOVA model. The balanced model is as follows:

$$y_{ij} = \mu + \alpha_i + \varepsilon_{ij}$$

$$i = 1, \ldots, g \qquad j = 1, \ldots, n \qquad N = n \cdot g$$

$$\alpha_i \overset{iid}{\sim} \mathcal{N}(0, \sigma_A^2) \qquad \varepsilon_{ij} \overset{iid}{\sim} \mathcal{N}(0, \sigma^2)$$

where g is the number of groups, n is the number of replicates per group, and N is the total number of replicates in the experiment. In the case of the unbalanced model, each group can have a different number of replicates n_i and the total number of replicates is $N = \sum_{i=1}^{g} n_i$.

Vector/matrix notation significantly facilitates the math that follows. This notation makes use of the direct sum denoted $\oplus$. The one-way ANOVA model can be represented in the following vector/matrix notation where bold lowercase characters represent vectors and bold uppercase characters represent matrices. The model has been written to allow the user to consider both balanced and unbalanced experiment designs.

$$\mathbf{y} = \mu \mathbf{1}_N + \mathbf{Z}\mathbf{a} + \mathbf{e}$$

where $\mathbf{Z} = \bigoplus_{i=1}^{g} \mathbf{1}_{n_i}$, $\mathbf{a} = \begin{bmatrix} \alpha_1 & \ldots & \alpha_g \end{bmatrix}'$ and $\mathbf{e}$ is an $N \times 1$ vector of the model errors. $\mathbf{a} \sim$

$\mathcal{N}_g\left(\mathbf{0}, \sigma_A^2 \bigoplus_{i=1}^{g} \mathbf{J}_{\mathbf{n_i}}\right)$ where $\mathbf{J}$ is a matrix of 1s of specified dimension and $\mathbf{e} \sim \mathcal{N}_N\left(\mathbf{0}, \sigma^2 \mathbf{I}_N\right)$. The distributions of $\mathbf{a}$ and $\mathbf{e}$ are independent.

By summing the variance of the distributions of $\mathbf{a}$ and $\mathbf{e}$, we get the probability model's variance matrix $\mathbf{V}$. If the structure of $\mathbf{V}$ is known, the model can be succinctly stated as $\mathbf{y} \sim \mathcal{N}_N(\mu \mathbf{1}_N, \mathbf{V})$ [18]. The methods demonstrated in this chapter depend on knowing the exact structure of $\mathbf{V}$ therefore we will show its derivation. This will be done to allow for both balanced and unbalanced designs.

$$
\begin{aligned}
\mathbf{V} = \operatorname{var}(\mathbf{y}) &= \operatorname{var}(\mu \mathbf{1}_N + \mathbf{Z}\mathbf{a} + \mathbf{e}) \\
&= \operatorname{var}(\mathbf{Z}\mathbf{a}) + \operatorname{var}(\mathbf{e}) \\
&= \mathbf{Z}\operatorname{var}(\mathbf{a})\mathbf{Z}' + \sigma^2 \mathbf{I}_N \\
&= \left(\bigoplus_{i=1}^{g} \mathbf{1}_{n_i}\right) \sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{1}_{n_i}\right)' + \sigma^2 \mathbf{I}_N \\
&= \sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{1}_{n_i}\right) \left(\bigoplus_{i=1}^{g} \mathbf{1}_{n_i}\right)' + \sigma^2 \mathbf{I}_N \\
&= \sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{1}_{n_i}\right) \left(\bigoplus_{i=1}^{g} \mathbf{1}'_{n_i}\right) + \sigma^2 \mathbf{I}_N \\
&= \sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{1}_{n_i} \mathbf{1}'_{n_i}\right) + \sigma^2 \mathbf{I}_N \\
&= \sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_i}\right) + \sigma^2 \mathbf{I}_N
\end{aligned}
\tag{2.1}
$$

When dealing with a balanced experiment design, all n_i are equal such that $n_i = n$. In this case, the Kronecker product, written $\otimes$, can be used instead of the direct sum and Equation 2.1 simplifies to the following:

$$
\mathbf{V} = \sigma_A^2 (\boldsymbol{I}_g \otimes \boldsymbol{J}_n) + \sigma^2 \boldsymbol{I}_N \tag{2.2}
$$

In order to conduct optimal design of experiments, it is necessary to derive the information matrix as that is the object that undergoes optimization. To derive the information matrix, we note that maximum likelihood estimators converge in distribution to a normal distribution with mean equal to the true parameter and variance equal to the inverse information matrix [19].

$$
\hat{\boldsymbol{\theta}}_{\mathrm{MLE}} \xrightarrow{d} \mathcal{N}(\boldsymbol{\theta}, \boldsymbol{\mathcal{I}}^{-1})
$$

The information matrix can be derived by solving for the Hessian of the negative log-likelihood function of the model in question. The probability density and likelihood function for the one-way ANOVA model is

$$L(\mu, \mathbf{V} \mid \mathbf{y}) = f(\mathbf{y} \mid \mu, \mathbf{V}) = \frac{1}{2\pi^{\frac{N}{2}}|\mathbf{V}|^{\frac{1}{2}}} e^{(\mathbf{y}-\mu\mathbf{1}_N)'\mathbf{V}^{-1}(\mathbf{y}-\mu\mathbf{1}_N)} \tag{2.3}$$

By taking the natural logarithm and multiplying by negative one, we get the negative log-likelihood function.

$$-l(L) = \frac{N}{2}\log(\pi) + \frac{1}{2}\log(|\mathbf{V}|) + \frac{1}{2}(\mathbf{y}-\mu\mathbf{1}_N)'\mathbf{V}^{-1}(\mathbf{y}-\mu\mathbf{1}_N) \tag{2.4}$$

The information matrix, the Hessian of the model's negative log-likelihood function, will take the following form:

$$\mathbf{H} = \begin{bmatrix} -(l(L))_{\sigma^2\sigma^2} & -(l(L))_{\sigma^2\sigma_A^2} \\ -(l(L))_{\sigma_A^2\sigma^2} & -(l(L))_{\sigma_A^2\sigma_A^2} \end{bmatrix}$$

Where our vector of parameters is $\boldsymbol{\theta} = \begin{bmatrix} \sigma^2 & \sigma_A^2 \end{bmatrix}'$ the following notation will be used for derivatives: $(\mathbf{X})_{\sigma^2,\sigma_A^2} = \frac{\partial^2 \mathbf{X}}{\partial\sigma^2\partial\sigma_A^2}$. Using this notation, the second derivative of the negative log-likelihood function is:

$$(-l(L))_{\theta_i\theta_j} = \frac{1}{2}(\log|\mathbf{V}|)_{\theta_i\theta_j} + \frac{1}{2}(\mathbf{y}-\mu\mathbf{1}_N)'(\mathbf{V}^{-1})_{\theta_i\theta_j}(\mathbf{y}-\mu\mathbf{1}_N) \tag{2.5}$$

Given this expression outputs a one-dimensional scalar, we can take the trace of its terms without changing the expression. Taking the trace allows the term to be reorganized cyclically. We will take the expectation as well to further simplify the expression.

$$(-l(L))_{\theta_i\theta_j} = \frac{1}{2}(\log|\mathbf{V}|)_{\theta_i\theta_j} + \frac{1}{2}\mathrm{tr}[E(\mathbf{y}-\mu\mathbf{1_N})(\mathbf{y}-\mu\mathbf{1}_N)'(\mathbf{V}^{-1})_{\theta_i\theta_j}] \tag{2.6}$$

We recognize $E(\mathbf{y}-\mu\mathbf{1_N})(\mathbf{y}-\mu\mathbf{1}_N)'$ to be the definition of model variance $\mathbf{V}$ which yields:

$$(-l(L))_{\theta_i\theta_j} = \frac{1}{2}(\log|\mathbf{V}|)_{\theta_i\theta_j} + \frac{1}{2}\mathrm{tr}[\mathbf{V}(\mathbf{V}^{-1})_{\theta_i\theta_j}] \tag{2.7}$$

Matrix calculus will be used to simplify the first and second terms of Equation 2.7.

2.1

Evaluating the first term of Equation 2.7: $(\log|\mathbf{V}|)_{\theta_i\theta_j}$

The following results will be required in order to evaluate this term [20]:

$$\log(|\mathbf{X}|)_y = \mathrm{tr}(\mathbf{X}^{-1}(\mathbf{X})_y) \tag{2.8}$$

$$(\mathbf{XY})_z = (\mathbf{X})_z\mathbf{Y} + \mathbf{X}(\mathbf{Y})_z \tag{2.9}$$

$$(\mathbf{X}^{-1})_y = -\mathbf{X}^{-1}(\mathbf{X})_y\mathbf{X}^{-1} \tag{2.10}$$

First, we must evaluate $(\log(|\mathbf{V}|)_{\theta_i}$. Using Equation 2.8 we get:

$$(\log|\mathbf{V}|)_{\theta_i} = \mathrm{tr}(\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}) \tag{2.11}$$

Now we must take the derivative of Equation 2.11 with respect to θ_j. This requires the use of the Equations 2.9 and 2.10.

$$(\log|\mathbf{V}|)_{\theta_i\theta_j} = (\mathrm{tr}(\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}))_{\theta_j} = \mathrm{tr}[-\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}\mathbf{V}^{-1}(\mathbf{V})_{\theta_i} + \mathbf{V}^{-1}(\mathbf{V})_{\theta_i\theta_j}] \tag{2.12}$$

2.2

Evaluating the second term of Equation 2.7: $\mathrm{tr}[\mathbf{V}(\mathbf{V}^{-1})_{\theta_i\theta_j}]$

In order to evaluate $(\mathbf{V}^{-1})_{\theta_i\theta_j}$ we must first know what $(\mathbf{V}^{-1})_{\theta_i}$ is. We can solve for it using the Equation 2.10.

$$(\mathbf{V}^{-1})_{\theta_i} = -\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1} \tag{2.13}$$

Now using Equation 2.9 we can evaluate $(\mathbf{V}^{-1})_{\theta_i\theta_j}$.

$$(\mathbf{V}^{-1})_{\theta_i\theta_j} = (-\mathbf{V}^{-1})_{\theta_j}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1} - \mathbf{V}^{-1}(\mathbf{V})_{\theta_i\theta_j}\mathbf{V}^{-1} - \mathbf{V}^{-1}(\mathbf{V})_{\theta_i}(\mathbf{V}^{-1})_{\theta_j} \tag{2.14}$$

Analogous to Equation 2.13, substitute $(\mathbf{V}^{-1})_{\theta_j} = -\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}\mathbf{V}^{-1}$

$$(\mathbf{V}^{-1})_{\theta_i\theta_j} = \mathbf{V}^{-1}(\mathbf{V})_{\theta_j}\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1} - \mathbf{V}^{-1}(\mathbf{V})_{\theta_i\theta_j}\mathbf{V}^{-1} + \mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}\mathbf{V}^{-1} \tag{2.15}$$

Remember that the term we are evaluating is $\mathrm{tr}[\mathbf{V}(\mathbf{V}^{-1})_{\theta_i\theta_j}]$. Now we will multiply $\mathbf{V}$ by $(\mathbf{V}^{-1})_{\theta_i\theta_j}$:

$$(\mathbf{V})_{\theta_j}\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1} - (\mathbf{V})_{\theta_i\theta_j}\mathbf{V}^{-1} + (\mathbf{V})_{\theta_i}\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}\mathbf{V}^{-1} \tag{2.16}$$

The trace can be applied linearly over addition and subtraction. Additionally, given the sum of each part will result in a one-dimensional object, the products within each trace can be rearranged cyclically.

$$\begin{aligned}
\mathrm{tr}[\mathbf{V}(\mathbf{V}^{-1})_{\theta_i\theta_j}] &= \mathrm{tr}[(\mathbf{V})_{\theta_j}\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1}] - \mathrm{tr}[(\mathbf{V})_{\theta_i\theta_j}\mathbf{V}^{-1}] + \mathrm{tr}[(\mathbf{V})_{\theta_i}\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}\mathbf{V}^{-1}] \\
&= \mathrm{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}] - \mathrm{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\theta_i\theta_j}] + \mathrm{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}] \\
&= \mathrm{tr}[2\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}] - \mathrm{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\theta_i\theta_j}] \\
&= \mathrm{tr}[2\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1}(\mathbf{V})_{\theta_j} - \mathbf{V}^{-1}(\mathbf{V})_{\theta_i\theta_j}]
\end{aligned} \tag{2.17}$$

2.3

Simplifying the Hessian

Using the results from (2.12) and (2.17), we can simplify the Hessian found in Equation 2.7

$$
\begin{aligned}
-(l(L))_{\theta_i\theta_j} &= \frac{1}{2}\text{tr}[-\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}\mathbf{V}^{-1}(\mathbf{V})_{\theta_i} + \mathbf{V}^{-1}(\mathbf{V})_{\theta_i\theta_j}] + \frac{1}{2}\text{tr}[2\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1}(\mathbf{V})_{\theta_j} - \mathbf{V}^{-1}(\mathbf{V})_{\theta_i\theta_j}] \\
&= \frac{1}{2}\{\text{tr}[-\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}\mathbf{V}^{-1}(\mathbf{V})_{\theta_i} + \mathbf{V}^{-1}(\mathbf{V})_{\theta_i\theta_j} + 2\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1}(\mathbf{V})_{\theta_j} - \mathbf{V}^{-1}(\mathbf{V})_{\theta_i\theta_j}\} \\
&= \frac{1}{2}\text{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\theta_i}\mathbf{V}^{-1}(\mathbf{V})_{\theta_j}] \qquad (2.18)
\end{aligned}
$$

Equation 2.18 is a generating equation for the elements of the Hessian of a nested variance component model. We will now use this equation to solve for those elements:

$$
\mathbf{H} = \begin{bmatrix} -(l(L))_{\sigma^2\sigma^2} & -(l(L))_{\sigma^2\sigma_A^2} \\ -(l(L))_{\sigma_A^2\sigma^2} & -(l(L))_{\sigma_A^2\sigma_A^2} \end{bmatrix}
$$

2.4

Solving for the elements of the one-way ANOVA Hessian

To solve for the elements of the Hessian, we require expressions for the variance and inverse variance of the model. We use an explicit expression for the variance and use software to solve for the inverse of that expression

$$
\mathbf{V} = \sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_i} \right) + \sigma^2 \mathbf{I}_N \qquad (2.19)
$$

$$
\mathbf{V}^{-1} = \left[\sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_i} \right) + \sigma^2 \mathbf{I}_N \right]^{-1} \qquad (2.20)
$$

where $\mathbf{J}$ is a matrix of 1s with specified dimension. If the model in question is a balanced design, then (2.19) simplifies to (2.2) and like in (2.20), its inverse is calculated using software. Given we have an explicit expression for the model variance matrix, we can calculate its derivatives with respect to the variance components.

$$
\begin{aligned}
(\mathbf{V})_{\sigma^2} &= \left(\sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_i} \right) + \sigma^2 \mathbf{I}_N \right)_{\sigma^2} \qquad (2.21) \\
&= \mathbf{I}_N
\end{aligned}
$$

$$
\begin{aligned}
(\mathbf{V})_{\sigma_A^2} &= \left(\sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_i}\right) + \sigma^2 \mathbf{I}_N\right)_{\sigma_A^2} \\
&= \left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_i}\right)
\end{aligned}
\tag{2.22}
$$

2.4.1

Solving for $-(l(L))_{\sigma^2\sigma^2}$

Using the derivative from (2.21) and noting that $\mathbf{V}$ is an $N \times N$ matrix, we get the following result:

$$
\begin{aligned}
-(l(L))_{\sigma^2\sigma^2} &= \frac{1}{2}\mathrm{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\sigma^2}\mathbf{V}^{-1}(\mathbf{V})_{\sigma^2}] \\
&= \frac{1}{2}\mathrm{tr}[\mathbf{V}^{-1}\mathbf{I}_N\mathbf{V}^{-1}\mathbf{I}_N] \\
&= \frac{1}{2}\mathrm{tr}[\mathbf{V}^{-1}\mathbf{V}^{-1}]
\end{aligned}
\tag{2.23}
$$

2.4.2

Solving for $-(l(L))_{\sigma^2\sigma_A^2}$

Using the derivatives from (2.21) and (2.22) and noting that $\mathbf{V}$ is an $N \times N$ matrix, we get the following result:

$$
\begin{aligned}
-(l(L))_{\sigma^2\sigma_A^2} &= \frac{1}{2}\mathrm{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\sigma^2}\mathbf{V}^{-1}(\mathbf{V})_{\sigma_A^2}] \\
&= \frac{1}{2}\mathrm{tr}\left[\mathbf{V}^{-1}\mathbf{I}_N\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_i}\right)\right] \\
&= \frac{1}{2}\mathrm{tr}\left[\mathbf{V}^{-1}\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_i}\right)\right]
\end{aligned}
\tag{2.24}
$$

2.4.3

Solving for $-(l(L))_{\sigma_A^2\sigma^2}$

Using the derivatives from (2.21) and (2.22) and noting that $\mathbf{V}$ is an $N \times N$ matrix, we get the following result:

$$
\begin{aligned}
-(l(L))_{\sigma_A^2\sigma^2} &= \frac{1}{2}\mathrm{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\sigma_A^2}\mathbf{V}^{-1}(\mathbf{V})_{\sigma^2}] \\
&= \frac{1}{2}\mathrm{tr}\left[\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\mathbf{J}_{n_i}\right)\mathbf{V}^{-1}\mathbf{I}_N\right] \\
&= \frac{1}{2}\mathrm{tr}\left[\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\mathbf{J}_{n_i}\right)\mathbf{V}^{-1}\right]
\end{aligned} \tag{2.25}
$$

2.4.4

Solving for $-(l(L))_{\sigma_A^2\sigma_A^2}$

Using the derivatives from (2.21) and (2.22) and noting that $\mathbf{V}$ is an $N \times N$ matrix, we get the following result:

$$
\begin{aligned}
-(l(L))_{\sigma_A^2\sigma_A^2} &= \frac{1}{2}\mathrm{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\sigma_A^2}\mathbf{V}^{-1}(\mathbf{V})_{\sigma_A^2}] \\
&= \frac{1}{2}\mathrm{tr}\left[\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\mathbf{J}_{n_i}\right)\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\mathbf{J}_{n_i}\right)\right]
\end{aligned} \tag{2.26}
$$

2.5

The information matrix for the one-way ANOVA model

By calculating the Hessian of the negative log likelihood function for the one-way ANOVA model, we have successfully derived the information matrix which can now be used to conduct optimal designs of experiments.

$$
\mathbf{H}\left(\sigma^2, \sigma_A^2, g, n_i \;\middle|\; \sum_{i=1}^{g} n_i = N\right) = \begin{bmatrix} \frac{1}{2}\mathrm{tr}[\mathbf{V}^{-1}\mathbf{V}^{-1}] & \frac{1}{2}\mathrm{tr}\left[\mathbf{V}^{-1}\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\mathbf{J}_{n_i}\right)\right] \\ \frac{1}{2}\mathrm{tr}\left[\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\mathbf{J}_{n_i}\right)\mathbf{V}^{-1}\right] & \frac{1}{2}\mathrm{tr}\left[\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\mathbf{J}_{n_i}\right)\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\mathbf{J}_{n_i}\right)\right] \end{bmatrix} \tag{2.27}
$$

In the following Chapter we will walk through the open-source tools within the ODVC package that allow practitioners to generate and compare the quality of experiment designs for one-way nested random effects models.

CHAPTER 3
R UTILITIES FOR ONE-WAY RANDOM EFFECTS MODELS

In this chapter we will explore certain scenarios involving the one-way nested random effects model and how tools in the ODVC R package can be used in an optimal design framework. Unlike a fixed effects model, this is a non-linear optimal design problem. That being the case, the optimal design depends on the parameters. This results in many dimensions that require exploration unlike the linear optimal design problem. We will explore how factors such as optimality criteria, sample sizes, and hypothesized variance component values, affect the optimal design choice in both balanced and unbalanced designs.

We use a random effect model rather than a fixed effect model when we have a large population of factor levels and will select a sample of them to study. Deciding on the number of factor levels from the population to sample—the number of groups—is the design exercise for random effects. An example of this type of scenario would be a heterogeneity study. If a lab wanted to measure the amount of a single element in a large bucket of mother material, they could do an experiment with a one-way random effect model. An analyst would homogenize the material and divide it into a large number of vials (e.g., 300). The large number of vials would be the population for the heterogeneity study. The number of vials selected for the experiment from the population of vials is a random sample and therefore the vials would contribute a random effect. The design exercise would be choosing the number of vials of material to include in the experiment. This would represent the number of groups. The number of measurements taken on each vial would be the number of replicates per group. Tools in the ODVC package can be used to determine whether it is more advantageous to take many measurements on a few vials or take a few measurements on many vials. This will largely depend on the hypothesized value of the variance components associated with the random sample of vials and the measurements on the vials.

Scenario 1

A statistician has been brought in to consult on the design of an experiment. They haven't spoken with the client in person yet and over the phone they have only provided a few details about the constraints of the experiment. However, the details they have provided have informed the statistician that the experiment will be a one-way random effects model and the variance component for the experimental factor is assumed to be about twice as big as the variance component for the random error. Using what information is available, the statistician loads the ODVC package to start exploring options. They begin a general exploration of one-way designs by using the `generate_designs_B` function which takes all combinations of number of groups, number of reps, and hypothesized values of the variance components expressed as the ratio $\tau = \frac{\sigma_A^2}{\sigma^2}$ to compute the D and A scores and relative efficiencies for this entire set of designs.

```
var_A = 2
candidates <- generate_designs_B(ngroups = c(2, 3, 4, 5, 6, 7, 8, 9, 10),
                                 nreps = c(2, 3, 4, 5, 6, 7, 8, 9, 10),
                                 taus = var_A)

head(candidates)
```

	N	a	n	tau	A_Score	D_Score	Relative.A.Efficiency	Relative.D.Efficiency
1	4	2	2	2	7.500000	6.2500000	12.05926	0.313600
2	6	2	3	2	6.000000	2.7222222	15.07407	0.720000
3	8	2	4	2	5.416667	1.6875000	16.69744	1.161481
4	10	2	5	2	5.100000	1.2100000	17.73420	1.619835
5	12	2	6	2	4.900000	0.9388889	18.45805	2.087574
6	14	2	7	2	4.761905	0.7653061	18.99333	2.561067

When the statistician has the opportunity to meet with the client in person, they are able to view the options the statistician has generated so far. After deciding on using the D criteria, the statistician builds a contour plot using the `contour_designs_B` function. This function builds two plots per combination of provided arguments. These plots show how the optimality score and relative efficiency changes as a function of the sample sizes. The very last contour plot generated from the function, see Figure 3.1, shows relative efficiency across the largest of the user selected parameter settings.

```
contours <- contour_designs_B(ngroups = c(2, 10),
                              nreps = c(2, 10),
                              taus = var_A, criteria = "D")
contours[[2]][[4]]
```

```
#[[2]] Returns a relative efficiency plot rather than the D score plot.
#[[4]] Returns the plot that crosses the last value of ngroups with the last value of nreps.
```

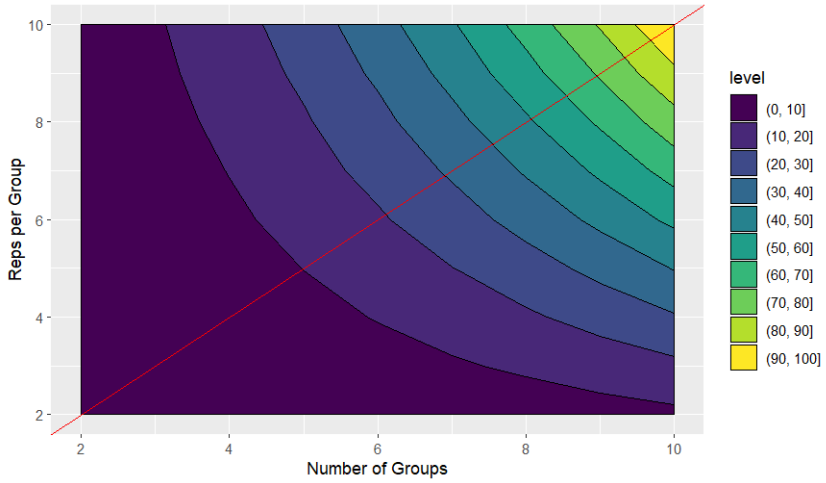

Figure 3.1: A contour plot that shows relative efficiency of designs up to $N = 100$ for $\tau = 2$.

The statistician explains that where the object we are optimizing, the information matrix, is a function of the design parameters — number of groups, number of replicates per group, and values of the variance components — logically it follows that larger experiments yield better designs. Within each band of the contour plot are designs that perform comparably well. The client explains that they would likely only be able to afford an experiment in the (10, 20] band. The statistician subsets these experiments and recalculates their relative efficiency to be based on just the designs within the subset. While looking at this set of experiments, the statistician and client note that the largest experiment is not necessarily the most efficient based on their specific number of groups, replicates per group, and value of τ.

```
candidates <- candidates[candidates$releff_D > 10 & candidates$releff_D <= 20, ]
OD_D <- min(candidates$D_Score)
OD_A <- min(candidates$A_Score)
candidates$releff_D <- 100 * OD_D / candidates$D_Score
candidates$releff_A <- 100 * OD_A / candidates$A_Score
candidates
```

```
    N   a   n   tau A_Score     D_Score     Relative.A.Efficiency    Relative.D.Efficiency
24  28  4   7   2   2.380952    0.19132653  50.40000                 51.62667
25  32  4   8   2   2.330357    0.16127232  51.49425                 61.24765
26  36  4   9   2   2.291667    0.13927469  52.36364                 70.92136
27  40  4   10  2   2.261111    0.12250000  53.07125                 80.63307
31  25  5   5   2   2.040000    0.19360000  58.82353                 51.02041
32  30  5   6   2   1.960000    0.15022222  61.22449                 65.75293
33  35  5   7   2   1.904762    0.12244898  63.00000                 80.66667
```

34	40	5	8	2	1.864286	0.10321429	64.36782		95.69946
39	24	6	4	2	1.805556	0.18750000	66.46154		52.68027
40	30	6	5	2	1.700000	0.13444444	70.58824		73.46939
41	36	6	6	2	1.633333	0.10432099	73.46939		94.68422
48	28	7	4	2	1.547619	0.13775510	77.53846		71.70370
49	35	7	5	2	1.457143	0.09877551	82.35294		100.00000
56	24	8	3	2	1.500000	0.17013889	80.00000		58.05581
57	32	8	4	2	1.354167	0.10546875	88.61538		93.65382
65	27	9	3	2	1.333333	0.13443073	90.00000		73.47688
74	30	10	3	2	1.200000	0.10888889	100.00000		90.71220

Upon looking at the designs within this band, the client says they would feel comfortable paying for an experiment of N=30. Knowing this the statistician can now narrow down their options. By calling the `subset_designs_B` function the statistician can show all candidate designs of size N=30 and recalculate relative efficiency based solely on this subset of designs.

```
candidates2 <- subset_designs_B(data = candidates, N = 30)
candidates2
```

	N	a	n	tau	A_Score	D_Score	Relative.A.Efficiency	Relative.D.Efficiency
32	30	5	6	2	1.96	0.1502222	61.22449	72.48521
40	30	6	5	2	1.70	0.1344444	70.58824	80.99174
74	30	10	3	2	1.20	0.1088889	100.00000	100.00000

The client observes that although all the candidate designs are balanced designs of size 30, clearly the design with the most groups, 10, and least reps per group, 3, is the best performing design. The statistician uses the `plot_design` function to provide a visualization of the experiment design (see Figure 3.2). The tree diagrams returned by this function identify the different groups in the top layer of the diagram, and the replicates nested within those groups in the bottom layer of the diagram. To facilitate identifying groups, replicates nested within the same group are highlighted in the same color. The client takes this design to their supervisors.

```
plot_design(n = rep(3, 10), a = 10, sig_a = var_A, error = 1, criteria = "D")
```

When the client speaks with their supervisor, the supervisor says that this design looks great, but they could actually afford 31 experimental runs. The supervisor wants to know if there is a

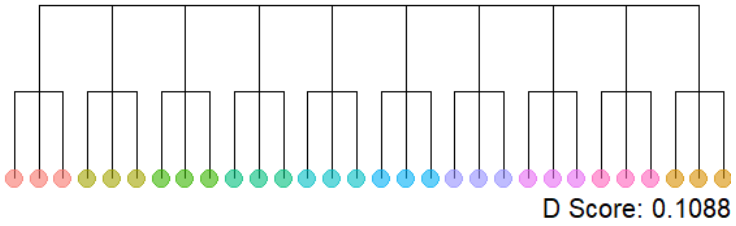

Figure 3.2: A tree diagram representing a balanced experiment with 10 groups, 3 replicates per group, $\tau = 2$, and scored on the D criteria.

significant increase in performance if one more replicate is added to the experiment. The client approaches the statistician and poses the question. The statistician points out that 31 runs will result in an unbalanced design, however, it is possible that it could perform better than the balanced design. They begin exploring options for a 31-run experiment. The statistician uses the `generate_designs_U` function to generate all unbalanced designs of size $N = 31$ with 10 groups.

```
candidates_u <- generate_designs_U(N = 31, a = 10, sig_a = var_A, error = 1)
```

By modifying the dataset to include relative efficiency with respect to the balanced $N = 30$ design, they can evaluate whether an $N = 31$ design would be worth considering.

```
tail(candidates_u[, c(1:6,9,10)])
```

	N	a	n_i	sig_a_sq	A_Score	D_Score	releff_A_balanced	releff_D_balanced
648	31	10	4 4 4 4 3 3 3 3 2 1 2		1.220422	0.1057647	98.32667	102.9539
649	31	10	4 4 4 4 3 3 3 2 2 2 2		1.204436	0.1044984	99.63172	104.2015
650	31	10	4 4 4 3 3 3 3 3 3 1 2		1.214013	0.1052171	98.84573	103.4897
651	31	10	4 4 4 3 3 3 3 3 2 2 2		1.198215	0.1039664	100.14895	104.7347
652	31	10	4 4 3 3 3 3 3 3 3 2 2		1.192068	0.1034407	100.66542	105.2669
653	31	10	4 3 3 3 3 3 3 3 3 3 2		1.185992	0.1029212	101.18113	105.7984

To get a better understanding of the options available to them, the statistician generates a scatter plot of dataset index against relative efficiency compared with the balanced design (see Figure 3.3). The dataset is structured such that in this design scenario, as index increases, the replicates become more balanced between groups. These plots are useful as they show how relative efficiency changes as the design approaches balance.

The statistician points out that the last design with 10 groups, 9 of which had 3 replicates and one with 4 replicates, is the best performing design. To see how this design performs compared to the previously selected N=30 design, the statistician calculates relative efficiency.

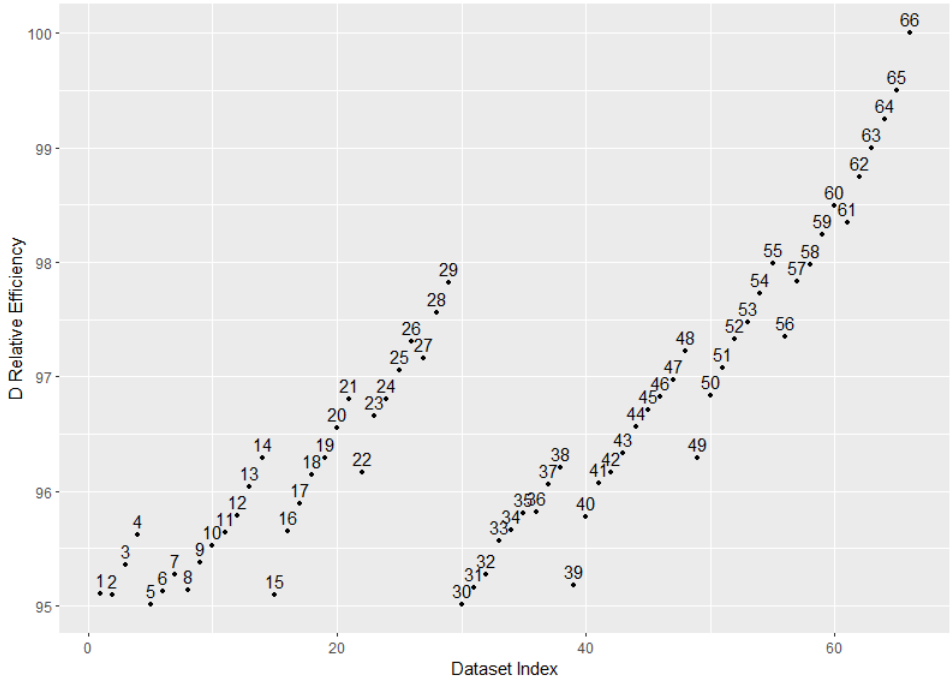

Figure 3.3: A scatter plot comparing relative efficiency against dataset index for unbalanced designs of size $N = 31$ with 10 groups to a balanced design of $N = 30$ with 10 groups. For this scenario $\tau = 2$ and designs are scored on the D criteria.

```
100 * candidates$D_Score[candidates$a == 10] / candidates_u$D_Score[66]
```

```
105.7984
```

The client observes about 5.8% increase in efficiency using the unbalanced design. They decide that is a justifiable increase and decide to go with the unbalanced design as seen in Figure 3.4.

```
plot_design(n = c(rep(3, 9), 4), a = 10, sig_a = var_A, error = 1, criteria = "D")
```

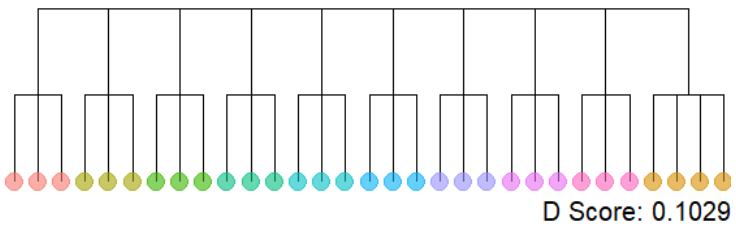

Figure 3.4: A tree diagram representing an unbalanced experiment with 10 groups such that 9 groups have 3 replicates and one group has 4 replicates. This design is for the scenario where $\tau = 2$ and is scored on the D criteria.

Scenario 2

An academic statistician wants to know how changing the value of $\tau = \frac{\sigma_A^2}{\sigma^2}$ affects the optimal design process for one-way nested random effects models. This is an important question as this is a non-linear design problem that is dependent on the value of the parameters: number of groups, number of replicates per group, and the values of the variance components. Before an experiment is done, the value of the variance components is unknown and hypothesized values must be used in their place. A proper understanding on how the true value of the variance components affects design choices is necessary when a researcher proposes a hypothesized value for that parameter. The statistician decides to begin with balanced designs of size N=24 and values of $\tau \in \{0.1, 0.5, 1, 2, 10\}$. They load the ODVC library in R, generate a dataset of candidate designs, and use the `compare_designs_B` function to create a dashboard visualization for both the D and A criteria.

```
var_A = c(0.1, 0.5, 1, 2, 10)
candidates <- generate_designs_B(ngroups = c(2, 3, 4, 6, 8, 12),
                                 nreps = c(2, 3, 4, 6, 8, 12),
                                 taus = var_A)
candidates <- subset_designs_B(data = candidates, N = 24)
compare_designs_B(designs = candidates, criteria = "D")
compare_designs_B(designs = candidates, criteria = "A")
```

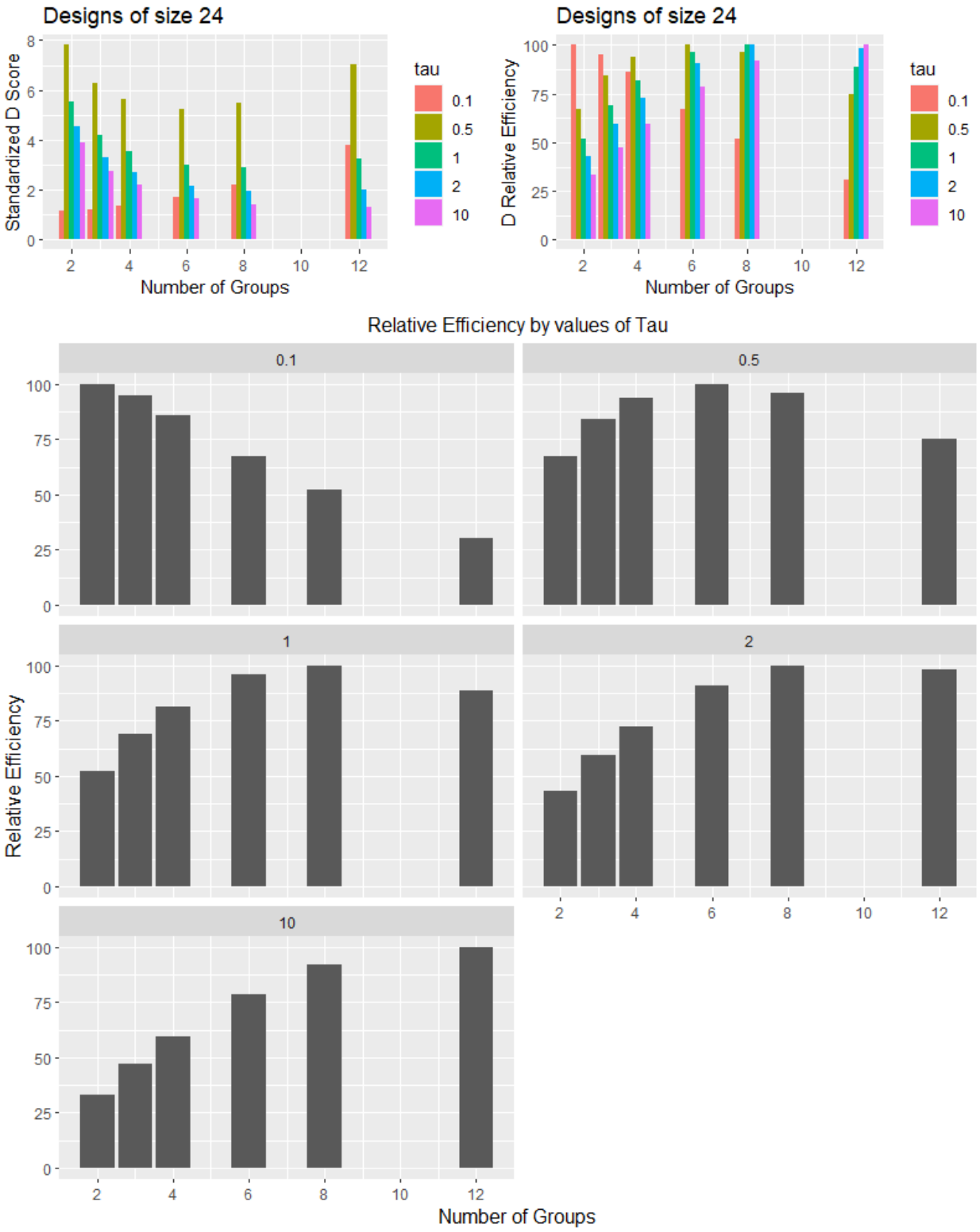

Figure 3.5: Comparing the relative efficiency of designs of size N=24 scored on the D criteria across various values of τ

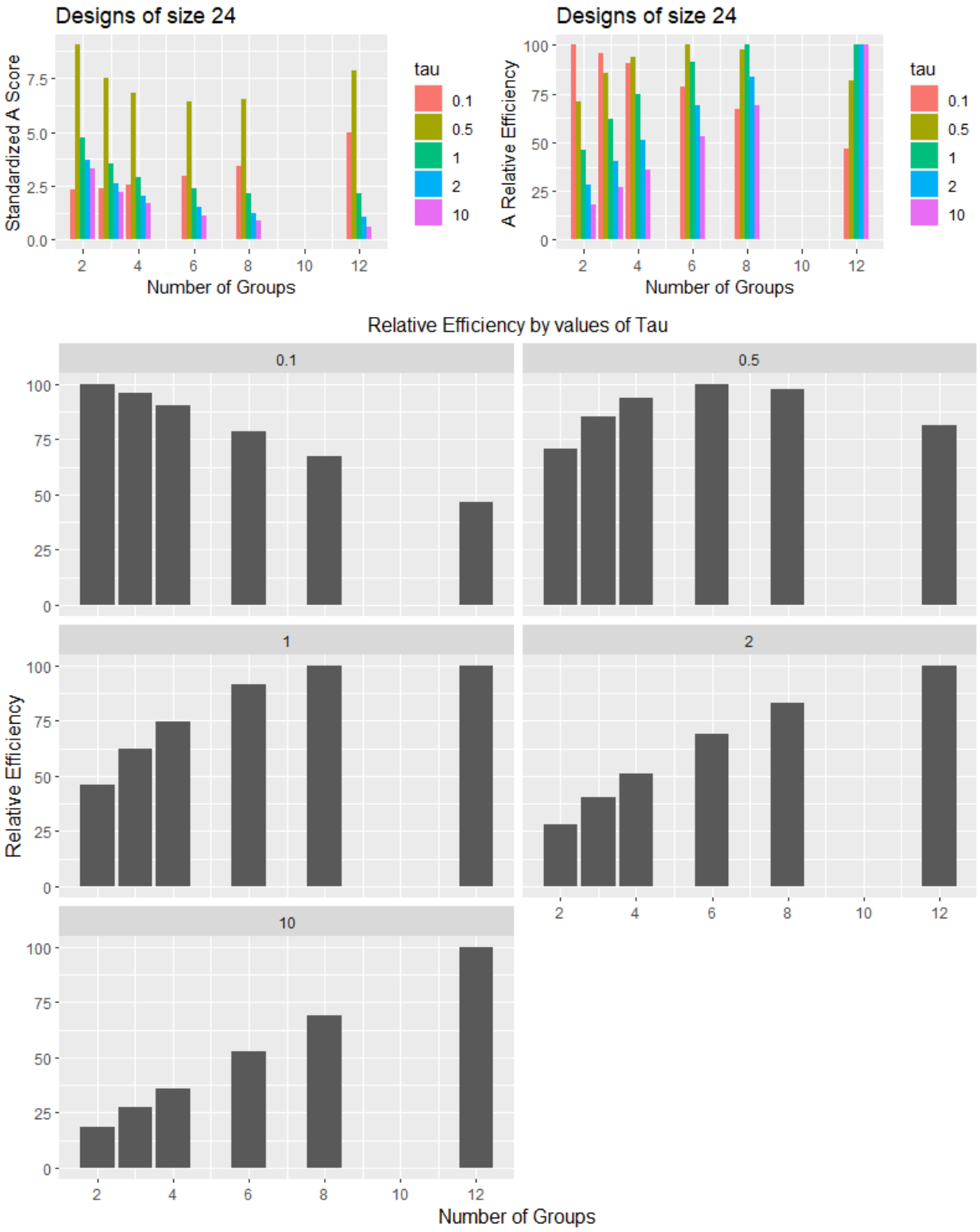

Figure 3.6: Comparing the relative efficiency of designs of size N=24 scored on the A criteria across various values of τ

$N = 24$		
τ	# of Groups in Optimal D Design	# of Groups in Optimal A Design
0.1	2	2
0.5	6	6
1	8	8 or 12
2	8	12
10	12	12

Table 3.1: The number of groups in the optimal design of size $N = 24$ given the value of variance components and optimality criteria.

The statistician observes the optimal design depends heavily on the value of τ and the criteria selected. Reference Table 3.1 to view a summary of the results.

The statistician now wants to know, in the case that and individual cannot do a balanced design, are there unbalanced designs of comparable quality? The statistician uses the `generate_designs_U` function to generate all designs of size N=24 with a specified number of groups. They then use the `compare_designs_U` function to view how many comparably well performing designs are available. This function facilitates identifying high performing designs by including a red reference line at 90% efficiency. They decide to explore the extreme values of $\tau \in \{0.1, 10\}$ for both the A and D criteria. The choice for the number of groups is made based on what the number of groups was in the optimal design for the balanced case. Design quality for the first case in which $\tau = 0.1$ and the design is scored on the D criteria is summarized in Figure 3.7.

```
candidates_u_1_D <- generate_designs_U(N = 24, a = 2, sig_a_sq = 0.1, error_sq = 1)
compare_designs_U(data = candidates_u_1_D, criteria = "D")
```

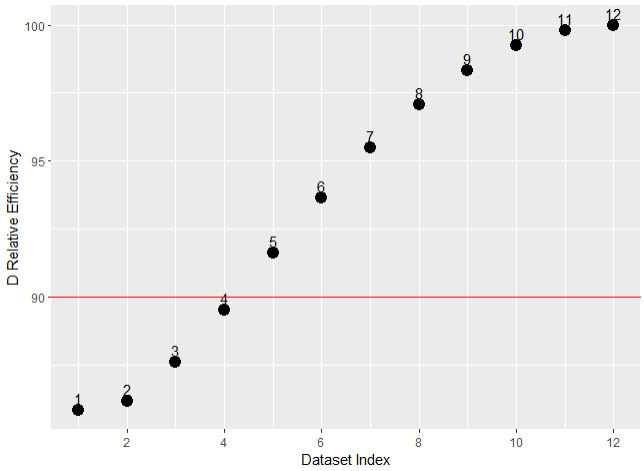

Figure 3.7: A scatter plot comparing relative efficiency against dataset index for designs of size $N = 24$ with 2 groups, $\tau = 0.1$, and scored on the D criteria.

The statistician sees in Figure 3.7 that the highest scoring design is the last one in the dataset with index 12. This so happens to be the balanced design. They observe that as the design approaches balance, the relative efficiency improves. Additionally, they note that there are various unbalanced designs that perform comparably well should the scenario occur that a balanced design is not possible. In Figure 3.8 we see the statistician's visualization of the top 6 performing designs.

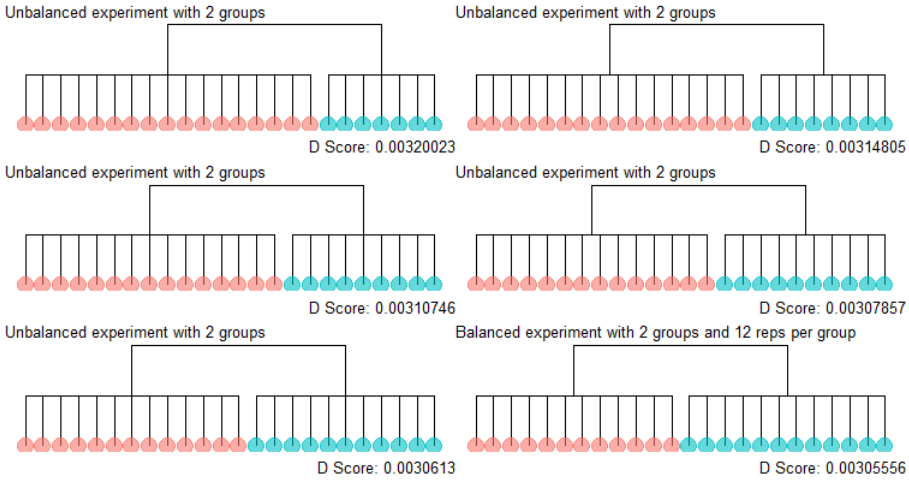

Figure 3.8: Top six performing designs of size $N = 24$ such that there are 2 groups, $\tau = 0.1$, and designs are scored on the D criteria.

They move on to the next case of designs with $N = 24$, where there are 12 groups, $\tau = 10$, and designs are scored on the D criteria. In Figure 3.9, the statistician takes advantage of the `top_5 = TRUE` argument for the `compare_designs_U` function to highlight the top 5 performing designs. Similar to previous cases, the optimal design is the last one in the dataset with index 77. This is the balanced design. The statistician observes that there are many unbalanced designs of comparable quality for circumstances that may prevent the use of a balanced design. The statistician visualizes the top 6 designs in Figure 3.10.

```
candidates_u_5_D <- generate_designs_U(N = 24, a = 12, sig_a_sq = 10, error_sq = 1)
compare_designs_U(data = candidates_u_5_D, criteria = "D", top_5 = TRUE)
```

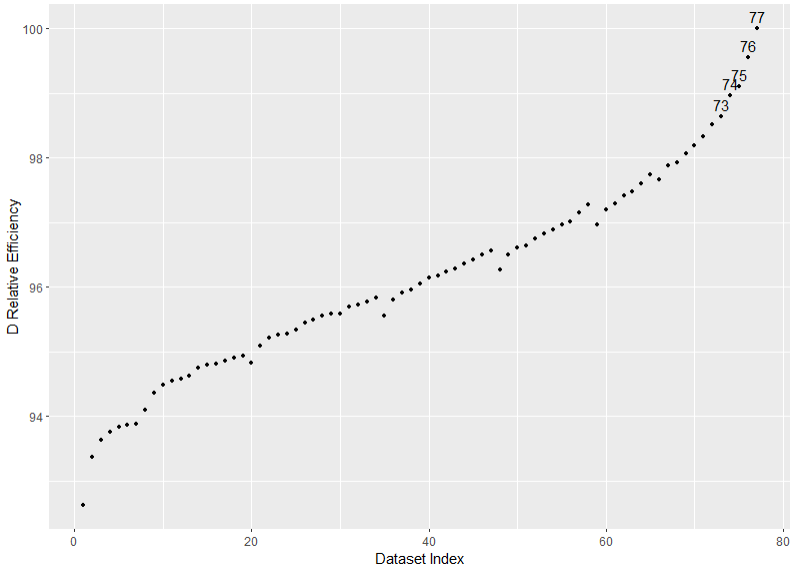

Figure 3.9: A scatter plot comparing relative efficiency against dataset index for designs of size $N = 24$ with 12 groups, $\tau = 10$, and designs are scored on the D criteria.

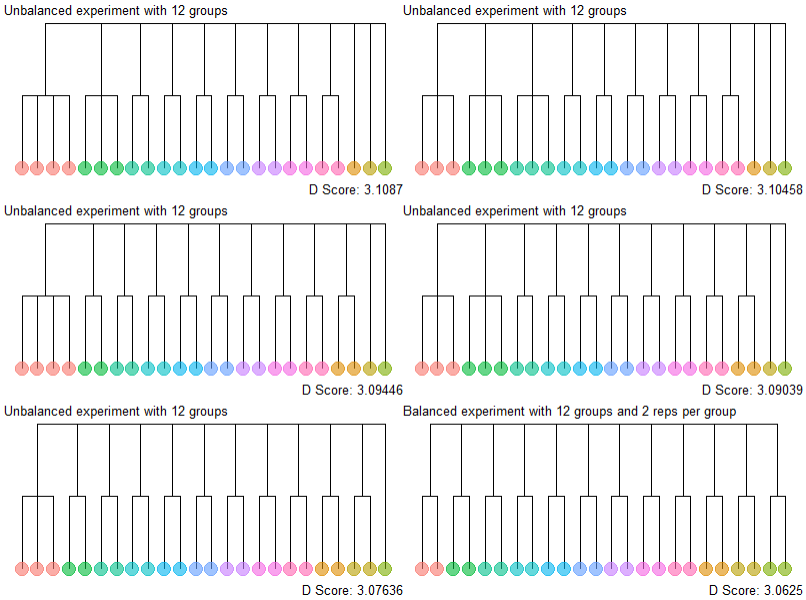

Figure 3.10: Top six performing designs of size $N = 24$ such that there are 12 groups, $\tau = 10$, and designs are scored on the D criteria.

The statistician now looks at the same cases but for the A criteria. In the case that $N = 24$, there are 2 groups, $\tau = 0.1$, and designs are scored on the A criteria we observe a similar pattern. In Figure 3.11, we see the best design is still the last one in the dataset which is the balanced design. One notable difference is that nearly all the designs are at least 97% efficient. This indicates that perhaps it is easier to find a high performing unbalanced design when the A criteria is used. The

statistician compares the top 6 designs in Figure 3.12.

```
candidates_u_1_A <- generate_designs_U(N = 24, a = 2, sig_a_sq = 0.1, error_sq = 1)
compare_designs_U(data = candidates_u_1_A, criteria = "A")
```

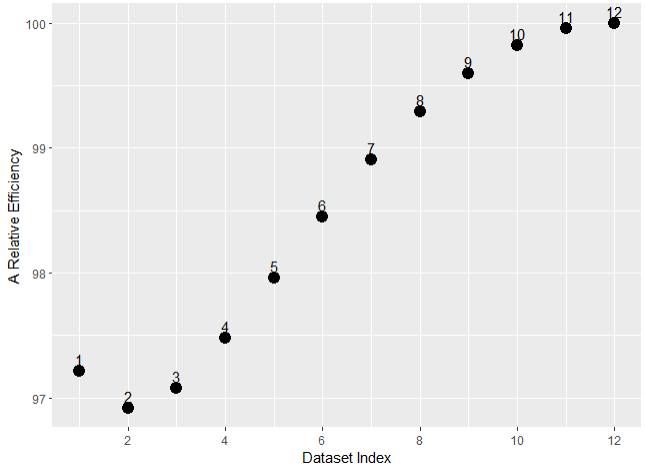

Figure 3.11: A scatter plot comparing relative efficiency against dataset index for design of size $N = 24$ with 2 groups, $\tau = 0.1$, and designs are scored on the A criteria.

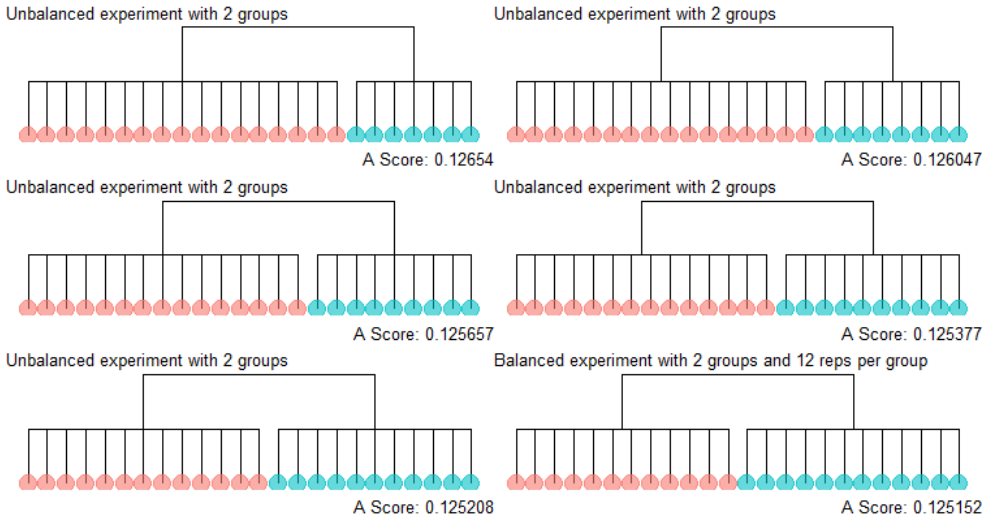

Figure 3.12: Top six performing designs of size $N = 24$ such that there are 2 groups, $\tau = 0.1$, and designs are scored on the A criteria.

The statistician now wants to check the last case when $N = 24$ with 12 groups, $\tau = 10$, and the designs are scored on the A criteria. In Figure 3.13, they note that like in previous cases, there are many comparably well performing unbalanced designs. They visualize the top 6 designs in Figure 3.14 to show that a well performing unbalanced design can easily be chosen should the occasion arise that a balanced design is not possible.

```
candidates_u_6_A <- generate_designs_U(N = 24, a = 12, sig_a_sq = 10, error_sq = 1)
compare_designs_U(data = candidates_u_6_A, criteria = "A", top_5 = TRUE)
```

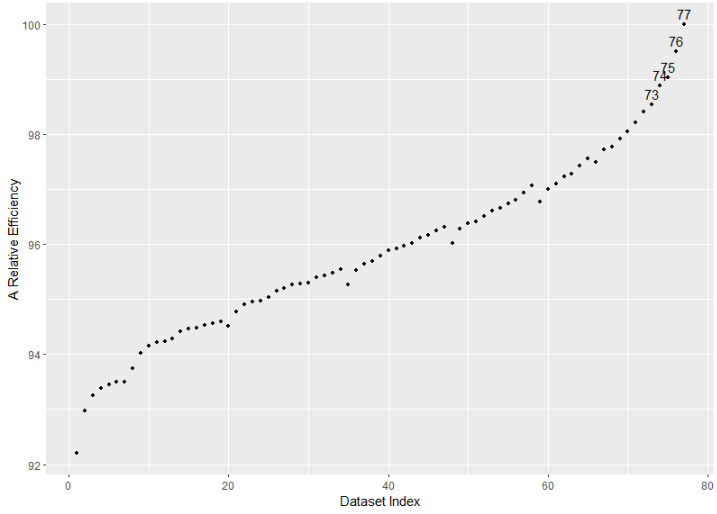

Figure 3.13: A scatter plot comparing relative efficiency against dataset index for designs of size $N = 24$ with 12 groups, $\tau = 10$, and designs are scored on the A criteria.

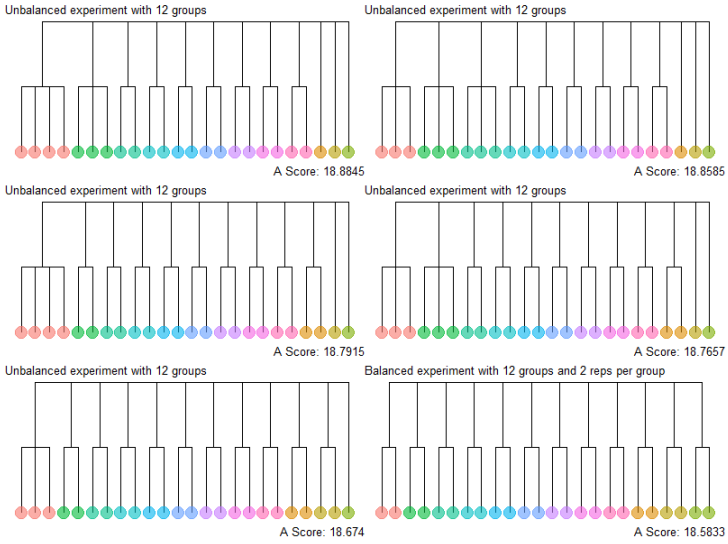

Figure 3.14: Top six performing designs of size $N = 24$ such that there are 12 groups, $\tau = 10$, and designs are scored on the A criteria.

As the statistician concludes this exploration, they are pleased to have made some valuable observations:

1. When planning for a balanced design, the optimal number of groups is highly dependent on the value of τ.

2. Occasionally there are balanced designs that perform equally as well. For example, when N=24, $\tau = 1$, and the A criteria is used, then either a design with 8 or 12 groups will perform equally well.

3. When planning for an unbalanced design, there are many potential unbalanced designs that perform comparably well to the optimal balanced design.

Conclusion

The tools available in the ODVC R package assist statisticians in both academic and applied scenarios to perform optimal design of experiments for one-way nested random effects models. We have highlighted how the `contour_designs_B` function can be used to explore how relative efficiency and optimality scores change based on the sample sizes of the experiment. By making use of Equation 2.18, the `generate_designs_B` and `generate_designs_U` functions can be used to generate all balanced or unbalanced designs, respectively, of a specified size and with respect to the users hypothesized variance component values. These tools score every design on two commonly used optimality criteria. This allows researchers to easily identify an optimal or high performing design based on the limitations of the setting in which they are conducting an experiment. The `compare_designs_B` and `compare_designs_U` functions return visualizations that allow researchers to compare the quality of competing designs for balanced and unbalanced designs respectively. Once a design has been chosen, it can be visualized using the `plot_design` function. In the next Chapter we will show how Equation 2.18 can be used to generate the information matrix for two-way nested random effects models.

CHAPTER 4

DERIVING THE INFORMATION MATRIX FOR THE TWO-WAY ANOVA MODEL

We will now take the findings of Chapter 2 and apply them to the two-way nested random effects model. The scalar version of this model is written as follows:

$$y_{ijk} = \mu + \alpha_i + \beta_{ij} + \varepsilon_{ijk}$$

$$i = 1, \ldots, g \qquad j = 1, \ldots, b_i \qquad k = 1, \ldots, n_{ij}$$

where g is the number of groups at the α level, b_i is the number of sub-groups per level of α, and n_{ij} is the number of reps per level of β nested in α. In vector/matrix notation, the model is:

$$\begin{aligned}\mathbf{y} &= \mu\mathbf{1}_N + \mathbf{Z}_1\mathbf{a} + \mathbf{Z}_2\mathbf{b} + \mathbf{e} \\ &= \mu\mathbf{1}_N + \left(\bigoplus_{i=1}^{g} \mathbf{1}_{n_{i\cdot}}\right)\begin{bmatrix} a_1 \\ \vdots \\ a_g \end{bmatrix} + \left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i} \mathbf{1}_{n_{ij}}\right)\begin{bmatrix} b_{11} \\ \vdots \\ b_{ij} \end{bmatrix} + \begin{bmatrix} e_{111} \\ \vdots \\ e_{ijk} \end{bmatrix}\end{aligned}$$

$\mathbf{a} \sim \mathcal{N}_g\left(\mathbf{0}, \sigma_A^2 \bigoplus_{i=1}^{g} \mathbf{J}_{\mathbf{n_i}\cdot}\right)$ where $\mathbf{J}$ is a matrix of 1s of specified dimension, $\mathbf{b} \sim \mathcal{N}_{\sum_{i=1}^{g} b_i}$ $\left(\mathbf{0}, \sigma_B^2 \bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i} \mathbf{J}_{n_{ij}}\right)$ where $\mathbf{J}$ is a matrix of 1s of specified dimension and $\mathbf{e} \sim \mathcal{N}_N\left(\mathbf{0}, \sigma^2\mathbf{I}_N\right)$. The distributions of $\mathbf{a}$, $\mathbf{b}$, and $\mathbf{e}$ are independent.

By summing the variance of the distributions of $\mathbf{a}$, $\mathbf{b}$ and $\mathbf{e}$, we get the probability model's variance matrix $\mathbf{V}$. If the structure of $\mathbf{V}$ is known, the model can be succinctly stated as $\mathbf{y} \sim \mathcal{N}_N(\mu\mathbf{1}_N, \mathbf{V})$ [18]. The methods demonstrated in this chapter depend on knowing the exact structure of $\mathbf{V}$ therefore we will show its derivation. This will be done to allow for both balanced and unbalanced designs.

$$
\begin{aligned}
\mathbf{V} = \mathrm{var}(\mathbf{y}) &= \mathrm{var}(\mu\mathbf{1}_N + \mathbf{Z}_1\mathbf{a} + \mathbf{Z}_2\mathbf{b} + \mathbf{e}) \\
&= \mathrm{var}(\mathbf{Z}_1\mathbf{a}) + \mathrm{var}(\mathbf{Z}_2\mathbf{b}) + \mathrm{var}(\mathbf{e}) \\
&= \mathbf{Z}_1\mathrm{var}(\mathbf{a})\mathbf{Z}_1' + \mathbf{Z}_2\mathrm{var}(\mathbf{b})\mathbf{Z}_2' + \sigma^2\mathbf{I}_N \\
&= \left(\bigoplus_{i=1}^{g}\mathbf{1}_{n_{i\cdot}}\right)\sigma_A^2\left(\bigoplus_{i=1}^{g}\mathbf{1}_{n_{i\cdot}}\right)' + \left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i}\mathbf{1}_{n_{ij}}\right)\sigma_B^2\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i}\mathbf{1}_{n_{ij}}\right)' + \sigma^2\mathbf{I}_N \\
&= \sigma_A^2\left(\bigoplus_{i=1}^{g}\mathbf{1}_{n_{i\cdot}}\right)\left(\bigoplus_{i=1}^{g}\mathbf{1}_{n_{i\cdot}}\right)' + \sigma_B^2\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i}\mathbf{1}_{n_{ij}}\right)\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i}\mathbf{1}_{n_{ij}}\right)' + \sigma^2\mathbf{I}_N \\
&= \sigma_A^2\left(\bigoplus_{i=1}^{g}\mathbf{1}_{n_{i\cdot}}\right)\left(\bigoplus_{i=1}^{g}\mathbf{1}'_{n_{i\cdot}}\right) + \sigma_B^2\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i}\mathbf{1}_{n_{ij}}\right)\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i}\mathbf{1}'_{n_{ij}}\right) + \sigma^2\mathbf{I}_N \\
&= \sigma_A^2\left(\bigoplus_{i=1}^{g}\mathbf{1}_{n_{i\cdot}}\mathbf{1}'_{n_{i\cdot}}\right) + \sigma_B^2\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i}\mathbf{1}_{n_{ij}}\mathbf{1}'_{n_{ij}}\right) + \sigma^2\mathbf{I}_N \\
&= \sigma_A^2\left(\bigoplus_{i=1}^{g}\mathbf{J}_{n_{i\cdot}}\right) + \sigma_B^2\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i}\mathbf{J}_{n_{ij}}\right) + \sigma^2\mathbf{I}_N
\end{aligned}
\tag{4.1}
$$

When dealing with a balanced experiment design, all $n_{i\cdot}$ are equal such that $n_{i\cdot} = b$. Additionally all n_{ij} are equal such that $n_{ij} = n$. In this case, the Kronecker product, written $\otimes$, can be used instead of the direct sum and (4.1) simplifies to the following [14]:

$$\mathbf{V} = (\mathbf{I}_g \otimes \mathbf{J}_b \otimes \mathbf{J}_n)\sigma_A^2 + (\mathbf{I}_g \otimes \mathbf{I}_b \otimes \mathbf{J}_n)\sigma_B^2 + (\mathbf{I}_g \otimes \mathbf{I}_b \otimes \mathbf{I}_n)\sigma^2$$

Given we have an explicit expression for our model variance, we can use the same generating function from (2.18) to solve for the elements of our Hessian taking into account that our vector of parameters is now $\mathbf{\Theta} = \begin{bmatrix}\sigma_A^2 & \sigma_B^2 & \sigma^2\end{bmatrix}'$.

$$\mathbf{H} = \begin{bmatrix} -(l(L))_{\sigma_A^2\sigma_A^2} & & \text{symmetric} \\ -(l(L))_{\sigma_A^2\sigma_B^2} & -(l(L))_{\sigma_B^2\sigma_B^2} & \\ -(l(L))_{\sigma_A^2\sigma^2} & -(l(L))_{\sigma_B^2\sigma^2} & -(l(L))_{\sigma^2\sigma^2} \end{bmatrix}$$

Substituting the elements of our Hessian with Equation 2.18 yields:

$$\mathbf{H} = \begin{bmatrix} \frac{1}{2}\text{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\sigma_A^2}\mathbf{V}^{-1}(\mathbf{V})_{\sigma_A^2}] & & \text{symmetric} \\ \frac{1}{2}\text{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\sigma_A^2}\mathbf{V}^{-1}(\mathbf{V})_{\sigma_B^2}] & \frac{1}{2}\text{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\sigma_B^2}\mathbf{V}^{-1}(\mathbf{V})_{\sigma_B^2}] & \\ \frac{1}{2}\text{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\sigma_A^2}\mathbf{V}^{-1}(\mathbf{V})_{\sigma^2}] & \frac{1}{2}\text{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\sigma_B^2}\mathbf{V}^{-1}(\mathbf{V})_{\sigma^2}] & \frac{1}{2}\text{tr}[\mathbf{V}^{-1}(\mathbf{V})_{\sigma^2}\mathbf{V}^{-1}(\mathbf{V})_{\sigma^2}] \end{bmatrix} \tag{4.2}$$

All that remains is to solve for the derivatives $(\mathbf{V})_{\sigma_A^2}$, $(\mathbf{V})_{\sigma_B^2}$, and $(\mathbf{V})_{\sigma^2}$

$$\begin{aligned} (\mathbf{V})_{\sigma_A^2} &= \left(\sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_{i\cdot}}\right) + \sigma_B^2 \left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i} \mathbf{J}_{n_{ij}}\right) + \sigma^2 \mathbf{I}_N\right)_{\sigma_A^2} \\ &= \left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_{i\cdot}}\right) \end{aligned} \tag{4.3}$$

$$\begin{aligned} (\mathbf{V})_{\sigma_B^2} &= \left(\sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_{i\cdot}}\right) + \sigma_B^2 \left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i} \mathbf{J}_{n_{ij}}\right) + \sigma^2 \mathbf{I}_N\right)_{\sigma_B^2} \\ &= \left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i} \mathbf{J}_{n_{ij}}\right) \end{aligned} \tag{4.4}$$

$$\begin{aligned} (\mathbf{V})_{\sigma^2} &= \left(\sigma_A^2 \left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_{i\cdot}}\right) + \sigma_B^2 \left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i} \mathbf{J}_{n_{ij}}\right) + \sigma^2 \mathbf{I}_N\right)_{\sigma^2} \\ &= \mathbf{I}_N \end{aligned} \tag{4.5}$$

If we now plug these derivatives into (4.2), we have the explicit expression for the two-way nested random effects model's information matrix.

$$\mathbf{H}(\sigma^2, \sigma_A^2, \sigma_B^2, g, b_i, n_{ij} | \sum_{i=1}^{g}\sum_{j=1}^{b_i} n_{ij} = N) =$$

$$\begin{bmatrix} \frac{1}{2}\text{tr}\left[\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_{i\cdot}}\right)\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_{i\cdot}}\right)\right] & & \text{symmetric} \\ \frac{1}{2}\text{tr}\left[\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_{i\cdot}}\right)\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i} \mathbf{J}_{n_{ij}}\right)\right] & \frac{1}{2}\text{tr}\left[\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i} \mathbf{J}_{n_{ij}}\right)\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i} \mathbf{J}_{n_{ij}}\right)\right] & \\ \frac{1}{2}\text{tr}\left[\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g} \mathbf{J}_{n_{i\cdot}}\right)\mathbf{V}^{-1}\mathbf{I}_N\right] & \frac{1}{2}\text{tr}\left[\mathbf{V}^{-1}\left(\bigoplus_{i=1}^{g}\bigoplus_{j=1}^{b_i} \mathbf{J}_{n_{ij}}\right)\mathbf{V}^{-1}\mathbf{I}_N\right] & \frac{1}{2}\text{tr}\left[\mathbf{V}^{-1}\mathbf{I}_N\mathbf{V}^{-1}\mathbf{I}_N\right] \end{bmatrix} \tag{4.6}$$

4.1

Validating coded implementation of the information matrix generating function

Given the purpose of the previously mentioned ODVC package is to allow users to do optimal design of experiments for nested random effects models, it is important to validate that the coded implementation of the information matrix generating function is accurate. Fortunately, there are computational checks for both the balanced and unbalanced case of the two-way nested model.

4.1.1

Validation for the balanced two-way nested model

To ensure that the coded implementation of Equation 2.18 in the ODVC package accurately calculates the information matrix for one-way and two-way nested random effects models, four different computational validations are tested. These validations can be found in the `tests` folder of the ODVC package. They check that the output of ODVC functions matches the expected output in the one-way and two-way settings for both balanced and unbalanced scenarios [13] [14].

4.2

Conclusion

In the following Chapter we will walk through the open-source tools built to allow practitioners to generate and compare the quality of experiment designs for the two-way nested random effects model. These tools will make use of the information matrix generating function that this chapter validates.

CHAPTER 5

R UTILITIES FOR TWO-WAY RANDOM EFFECTS MODELS

5.1

Introduction

In this chapter we will walk through three analyses of two-way nested random effect designs in which we search for optimal designs over 25 combinations of values of $\rho_1 = \frac{\sigma_A^2}{\sigma^2}$ and $\rho_2 = \frac{\sigma_B^2}{\sigma^2}$. Note that in each scenario, $\sigma^2 = 1$ to facilitate comparing the ratios.

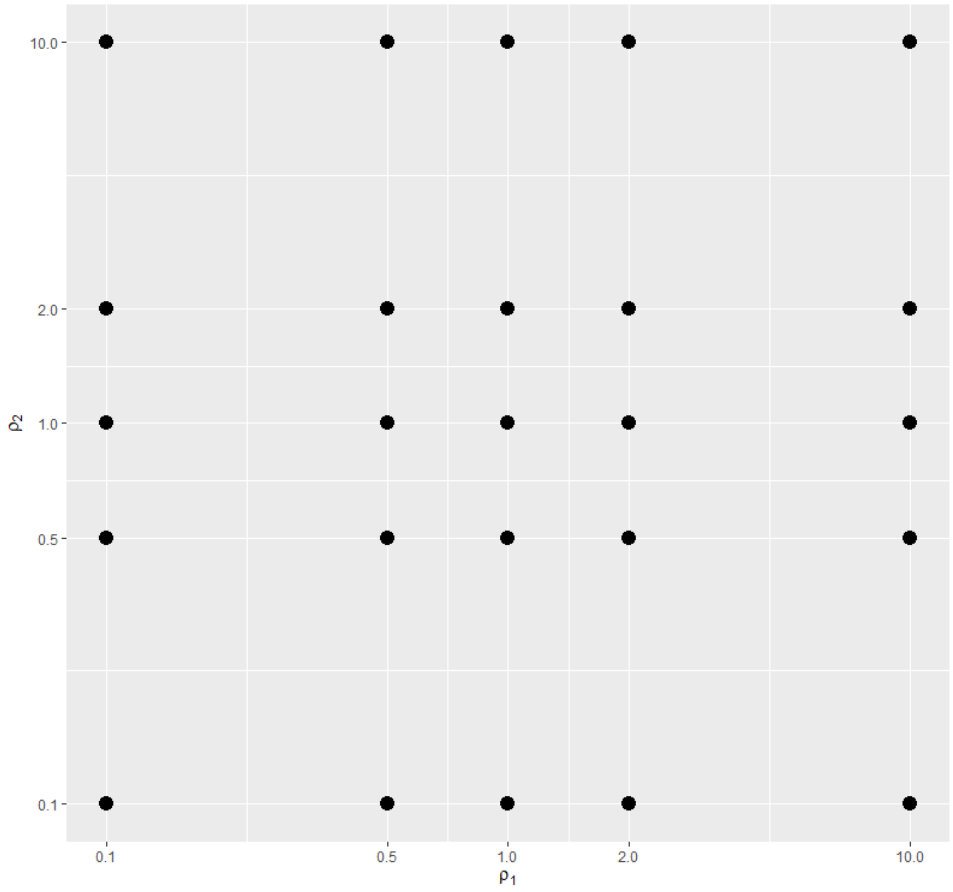

Figure 5.1: A 25-point grid of values on the log scale of ρ_1 and ρ_2 over which we will search for optimal designs.

These analyses are conducted using two different classes of experiment designs called $\mathcal{C}_{3,2}$ and $\mathcal{C}_{3,3}$. The first subscript denotes the number of variance components and the second subscript denotes the maximum number of subgroups and replicates per subgroup. Within each class exists a finite number of unique structures called atoms. The $\mathcal{C}_{3,2}$ and $\mathcal{C}_{3,3}$ classes have 5 and 19 atoms respectively. A collection of atoms is an experiment [16]. See Figures 5.2 and 5.3 for all atoms within both classes.

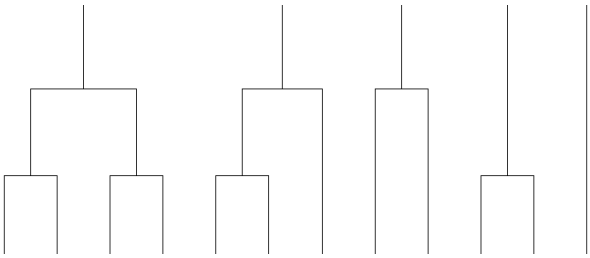

Figure 5.2: All 5 atoms from $\mathcal{C}_{3,2}$

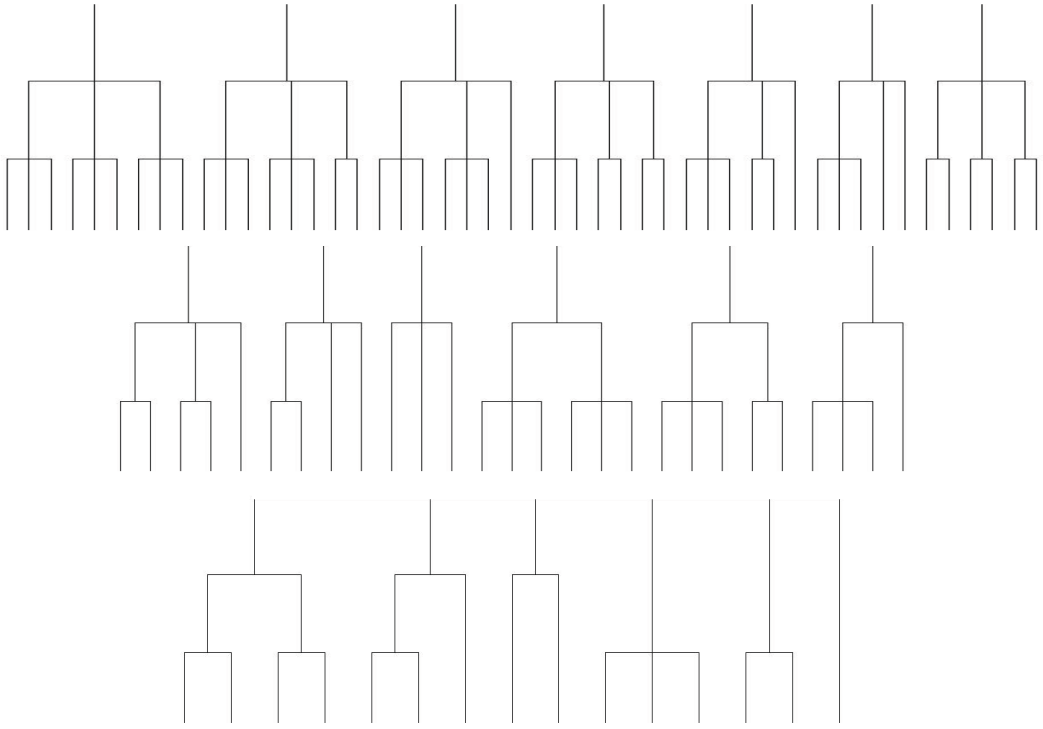

Figure 5.3: All 19 atoms from $\mathcal{C}_{3,3}$

We conduct our search for optimal designs over the 25 combinations of values of ρ_1 and ρ_2 within the following scenarios: ($\mathcal{C}_{3,2}$, $N = 12$), ($\mathcal{C}_{3,2}$, $N = 24$), and ($\mathcal{C}_{3,3}$, $N = 12$). For each analysis, we generate all designs of size N from the selected class, then return only the designs that include

adequate degrees of freedom to estimate all variance components. The designs are then scored on the D and A criteria. Relative efficiency to the optimal design is then calculated for both criteria. To build the datasets of designs for each experiment, the following function can be used from the ODVC package:

```
generate_two_way_designs(N = 24, s = 3, sig_a_sq = 0.1, sig_b_sq = 0.1, error_sq = 1)
```

where `s` refers to which class of experiments to build designs from. A value of `s = 2` indicates to build experiments from $\mathcal{C}_{3,2}$ while `s = 3` indicates to build experiments from $\mathcal{C}_{3,3}$.

Optimal design of experiments for random effects models is a combinatorial problem by nature. Given that the information matrix is a function of sample sizes within the experiment, the optimization routine involves generating all experiments of size N from a certain class. The number of experiments possible is a function of both the number of atoms within the class and the total number of replicates. As both numbers increase, the quantity of possible experiments grows exceptionally fast. That being said, researchers exploring this problem are limited by the computational resources available to them.

5.2

Analyses for designs of size N=12 generated from $\mathcal{C}_{3,2}$

The dataset of designs of size N=12 built from the class $\mathcal{C}_{3,2}$ has 76 designs in total. Experiments from this dataset will be referred to by their row index. The results of this 25-point analysis are summarized in Table 5.1. Some key findings include that for the D criteria, the balanced design with index 1 is the optimal design in all cases except for those which σ_B^2 is much greater than the other two variance components. In that case, design 3 is the optimal design. However, for the A criteria there is much more variety in optimal designs. Where only two designs were found to be optimal for the D criteria with this set of parameters, 8 designs were found to be optimal for the A criteria. See Figure 5.4 to reference the optimal designs from this analysis.

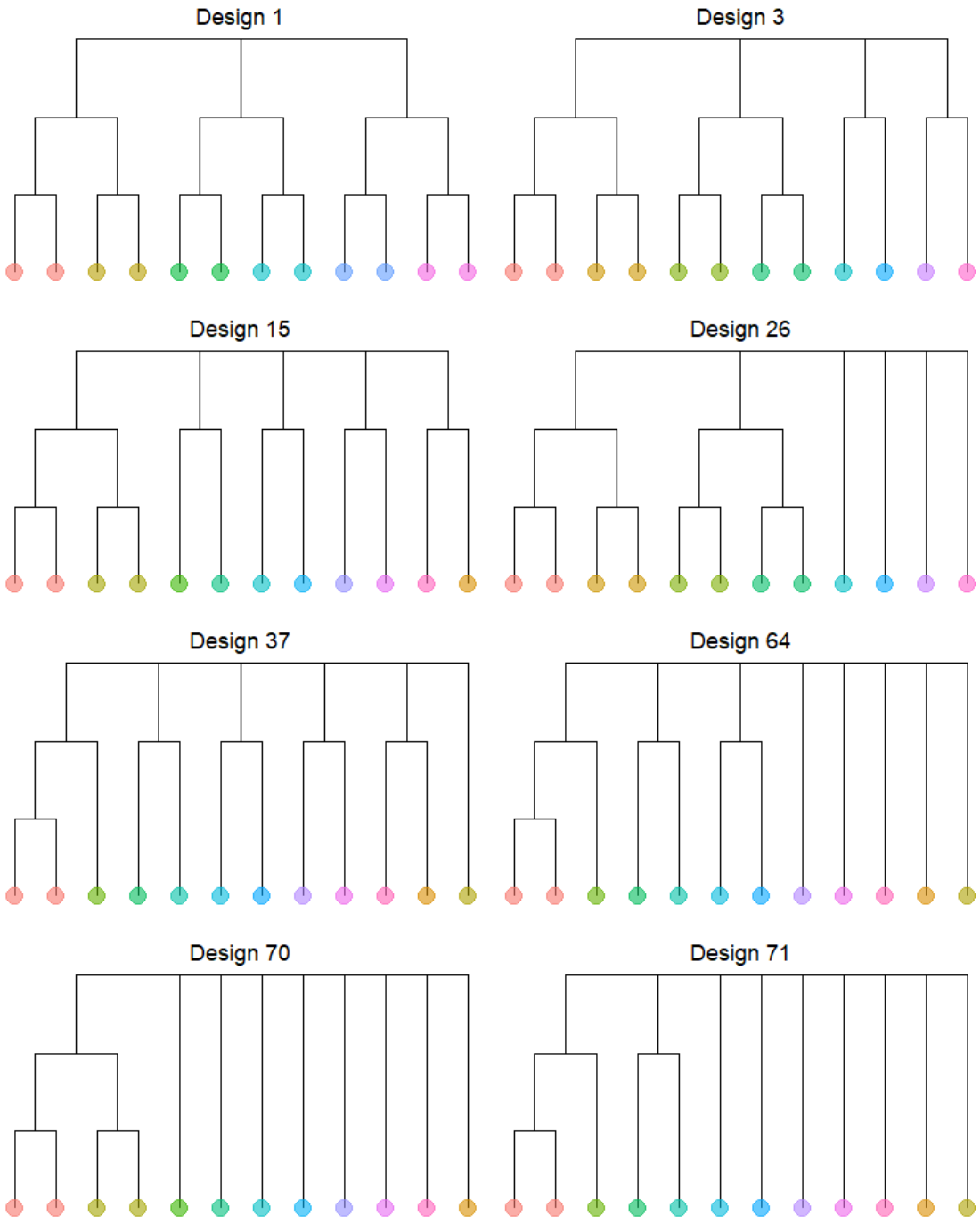

Figure 5.4: Designs of size $N = 12$ from $\mathcal{C}_{3,2}$ that were found to be optimal for at least one combination of the prespecified values of ρ_1 and ρ_2.

***D* Criteria**				***A* Criteria**			
ρ_1	ρ_2	Optimal Design Index	# $\geq 90\%$ Efficient	ρ_1	ρ_2	Optimal Design Index	# $\geq 90\%$ Efficient
0.1	0.1	1	1	0.1	0.1	1	1
0.1	0.5	1	1	0.1	0.5	1	1
0.1	1	1	1	0.1	1	1	5
0.1	2	1	1	0.1	2	3	11
0.1	10	3	4	0.1	10	15	4
0.5	0.1	1	1	0.5	0.1	1	1
0.5	0.5	1	1	0.5	0.5	1	2
0.5	1	1	1	0.5	1	1	5
0.5	2	1	1	0.5	2	3	10
0.5	10	3	4	0.5	10	15	4
1	0.1	1	1	1	0.1	1	9
1	0.5	1	1	1	0.5	1	7
1	1	1	1	1	1	3	7
1	2	1	4	1	2	3	10
1	10	3	4	1	10	15	4
2	0.1	1	1	2	0.1	26	29
2	0.5	1	1	2	0.5	3	25
2	1	1	1	2	1	3	18
2	2	1	5	2	2	15	9
2	10	3	4	2	10	15	4
10	0.1	1	2	10	0.1	70	10
10	0.5	1	2	10	0.5	70	12
10	1	1	4	10	1	71	21
10	2	1	7	10	2	64	20
10	10	3	3	10	10	37	4

Table 5.1: Results from a search for optimal designs of size $N = 12$ from the $C_{3,2}$ class over a 25-point grid of values for ρ_1 and ρ_2. This search was conducted for both the D and A criteria. The number of designs with relative efficiency greater or equal to 90% is also reported for each combination of ρ_1 and ρ_2.

5.3

Analyses for designs of size N=24 generated from $\mathcal{C}_{3,2}$

The dataset of designs of size N=24 built from the class $\mathcal{C}_{3,2}$ has 672 designs in total. The results of this 25-point analysis are summarized in Table 5.2. Similar to the previous case, we see that under the D criteria, the only time the balanced design is not optimal is when σ_B^2 is much greater than the other two variance components. We also see that under the A criteria, there is much more variation in which design is optimal. Where only three designs are optimal under the D criteria for this set of design parameters, 10 are optimal under the A criteria. The visualization of these designs, Figure 6.2, can be found in appendix A for reference.

***D* Criteria**				***A* Criteria**			
ρ_1	ρ_2	Optimal Design Index	# $\geq 90\%$ Efficient	ρ_1	ρ_2	Optimal Design Index	# $\geq 90\%$ Efficient
0.1	0.1	1	1	0.1	0.1	1	5
0.1	0.5	1	1	0.1	0.5	1	8
0.1	1	1	2	0.1	1	1	20
0.1	2	1	7	0.1	2	15	65
0.1	10	15	28	0.1	10	216	15
0.5	0.1	1	1	0.5	0.1	1	9
0.5	0.5	1	1	0.5	0.5	1	32
0.5	1	1	5	0.5	1	1	5
0.5	2	1	7	0.5	2	49	55
0.5	10	15	28	0.5	10	216	15
1	0.1	1	1	1	0.1	1	53
1	0.5	1	3	1	0.5	1	42
1	1	1	6	1	1	3	55
1	2	1	15	1	2	49	54
1	10	15	28	1	10	216	15
2	0.1	1	4	2	0.1	257	286
2	0.5	1	5	2	0.5	15	218
2	1	1	7	2	1	49	120
2	2	1	21	2	2	49	65
2	10	15	28	2	10	216	15
10	0.1	1	9	10	0.1	666	54
10	0.5	1	17	10	0.5	643	103
10	1	1	29	10	1	625	149
10	2	3	37	10	2	564	180
10	10	15	32	10	10	216	22

Table 5.2: Results from a search for optimal designs of size $N = 24$ from the $C_{3,2}$ class over a 25-point grid of values for ρ_1 and ρ_2. This search was conducted for both the D and A criteria. The number of designs with relative efficiency greater or equal to 90% is also reported for each combination of ρ_1 and ρ_2.

5.4

Analyses for designs of size N=12 generated from $\mathcal{C}_{3,3}$

The dataset of designs of size N=12 built from the class $\mathcal{C}_{3,3}$ has 709 designs in total. The results of this 25-point analysis are summarized in Table 5.3. Unlike the previous two analyses using $\mathcal{C}_{3,2}$, there is much more variation under the D criteria of optimal designs for this set of parameters. Under the D criteria in the previous two analyses, we've seen that the optimal design is the balanced design except for the case in which σ_B^2 is much greater than the other two variance components. It seems that under the D criteria, the choice of optimal design is more sensitive to the value of σ^2 than the other two variance components. Where a balanced design allocates the most degrees of freedom to the estimation of σ^2, it makes sense that it is often optimal under the D criteria. However, within the $\mathcal{C}_{3,3}$ class, there are several ways to make a balanced experiment of size N=12. Additionally, there are various unbalanced designs that still allocate more degrees of freedom for the

the estimation of σ^2. Which one is optimal depends on the values of ρ_1 and ρ_2.

Again, we see that under the A criteria, there is much more variation in which design is optimal. Where 9 designs are optimal under the D criteria for this set of design parameters, 14 are optimal under the A criteria. The visualization of these designs, Figures 6.3 and 6.4, can be found in appendix A for reference.

***D* Criteria**				***A* Criteria**			
ρ_1	ρ_2	Optimal Design Index	# $\geq 90\%$ Efficient	ρ_1	ρ_2	Optimal Design Index	# $\geq 90\%$ Efficient
0.1	0.1	3	4	0.1	0.1	3	12
0.1	0.5	16	10	0.1	0.5	16	19
0.1	1	16	3	0.1	1	16	10
0.1	2	16	5	0.1	2	80	45
0.1	10	16	45	0.1	10	233	14
0.5	0.1	18	10	0.5	0.1	18	36
0.5	0.5	16	12	0.5	0.5	16	21
0.5	1	16	5	0.5	1	16	22
0.5	2	16	7	0.5	2	80	27
0.5	10	80	45	0.5	10	233	14
1	0.1	18	8	1	0.1	138	176
1	0.5	16	13	1	0.5	86	158
1	1	16	7	1	1	78	92
1	2	16	7	1	2	80	27
1	10	80	45	1	10	233	14
2	0.1	20	9	2	0.1	574	178
2	0.5	16	37	2	0.5	333	237
2	1	16	18	2	1	49	120
2	2	16	22	2	2	80	76
2	10	80	47	2	10	233	14
10	0.1	139	2	10	0.1	702	18
10	0.5	139	9	10	0.5	702	24
10	1	195	61	10	1	703	53
10	2	86	93	10	2	690	63
10	10	78	57	10	10	233	30

Table 5.3: Results from a search for optimal designs of size $N = 12$ from the $C_{3,3}$ class over a 25-point grid of values for ρ_1 and ρ_2. This search was conducted for both the D and A criteria. The number of designs with relative efficiency greater or equal to 90% is also reported for each combination of ρ_1 and ρ_2.

5.5

The Allocation of Degrees of Freedom

What becomes apparent when exploring optimal design for the two-way nested random effects model is that the allocation of degrees of freedom is incredibly important. In a classical design scenario, it is common to default to a balanced design. However, when random effects are included, a balanced design allocates the majority of degrees of freedom to the estimation of the residual error variance component. Hence, the suggestion of staggered nested designs has been put forth to better

balance degrees of freedom for the precise estimation of all variance components [21]. However, when it is hypothesized that one variance component is significantly larger than the others, it would be advantageous to allocate more degrees of freedom for the estimation of that variance component. The benefit of the ODVC package is that it allows for easy exploration of experiment designs based on the sample sizes and hypothesized values of the variance components.

Consider the design scenario in which a researcher can afford 12 experiment runs, the D criterion is preferred, they hypothesize that σ_A^2 is about half the value of σ^2, and they hypothesize that σ_B^2 is about ten times the value of σ^2. Using the ODVC package, they run the following code:

```
N12_0.5.10_D <- generate_two_way_designs(N = 12, s = 2,
                    sig_a_sq = 0.5, sig_b_sq = 10, error_sq = 1)
compare_designs_U(data = N12_0.5_10, criteria = "D")
```

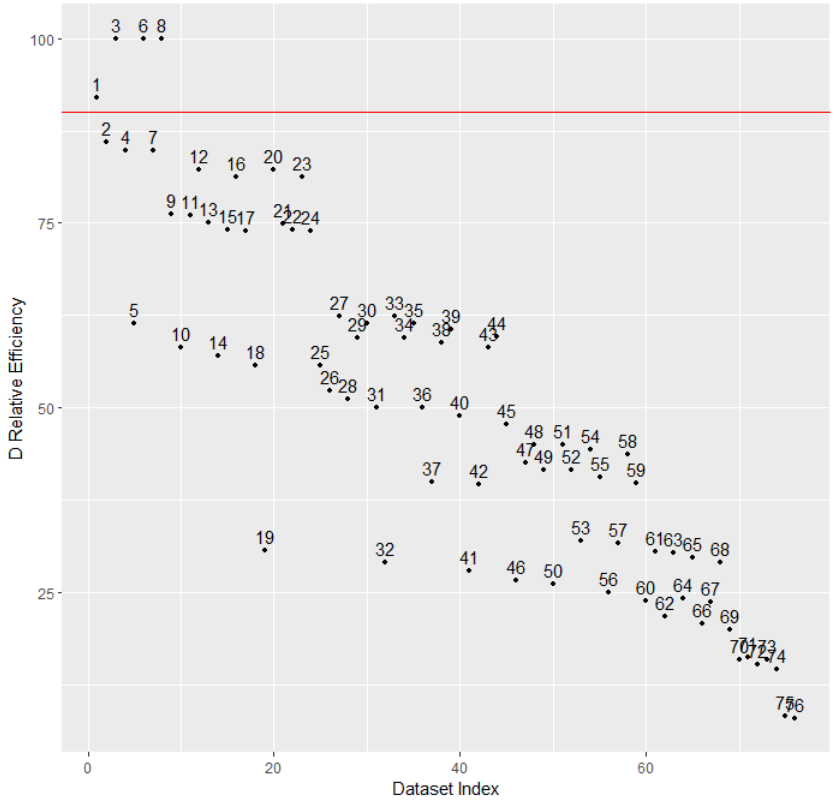

Figure 5.5: A scatter plot comparing the D relative efficiency of designs of size N=12 from $\mathcal{C}_{3,2}$ against dataset index with $\sigma_A^2 = 0.5$, $\sigma_B^2 = 10$, and $\sigma^2 = 1$.

We see that under these specific design parameters, designs 3, 6, and 8 perform nearly equally as well. Upon visualizing these designs, see Figure 5.6, we see that the allocation of degrees of freedom is almost equal between variance components. If a researcher used the balanced design,

design 1 in Figure 5.4, there would be 2, 3, and 6 degrees of freedom for the estimation of σ_A^2, σ_B^2, and σ^2 respectively. This would result in less precise estimation of the variance components under these specific design parameters. In Figure 5.6 we can see how designs 3, 6, and 8 more allocate 3, 4, and 4 degrees of freedom for the estimation of σ_A^2, σ_B^2, and σ^2 respectively. Where σ_B^2 is the largest source of variance, these designs are about 8% more efficient than the balanced design.

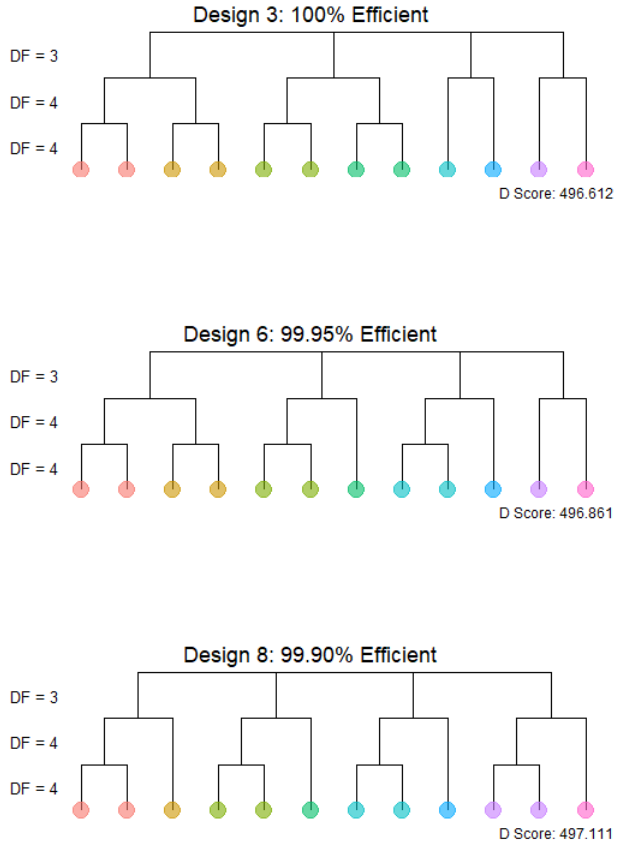

Figure 5.6: Top 3 performing designs of size $N = 12$ from $\mathcal{C}_{3,2}$ with $\sigma_A^2 = 0.5, \sigma_B^2 = 10$, and $\sigma^2 = 1$

5.6

Conditions in which staggered nested designs are highly efficient

Given that optimal design for random effects models is dependent on the allocation of degrees of freedom, a useful heuristic to know is when is a staggered nested design—a design in which the degrees of freedom are approximately equally distributed—is highly efficient. A design will be considered highly efficient if its relative efficiency is greater than or equal to 95%. For the sake of

this exploration, we will consider a staggered nested design a design built entirely of the atom in Figure 5.7:

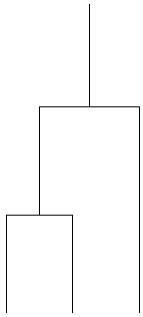

Figure 5.7: Atom from $\mathcal{C}_{3,2}$ that builds a staggered nested design

When evaluating designs of size $N = 12$ from the $\mathcal{C}_{3,2}$ class, we see that under the D criteria, staggered nested designs in which ρ_2 is larger than ρ_1 are often highly efficient. Under the A criteria for the same parameters, we see a lot more variation in when the staggered nested design is highly efficient. There are cases in which it is highly efficient when ρ_2 is larger than ρ_1 and vice versa. See Figure 5.8 to see specific cases in which the staggered nested design is highly efficient under these parameters.

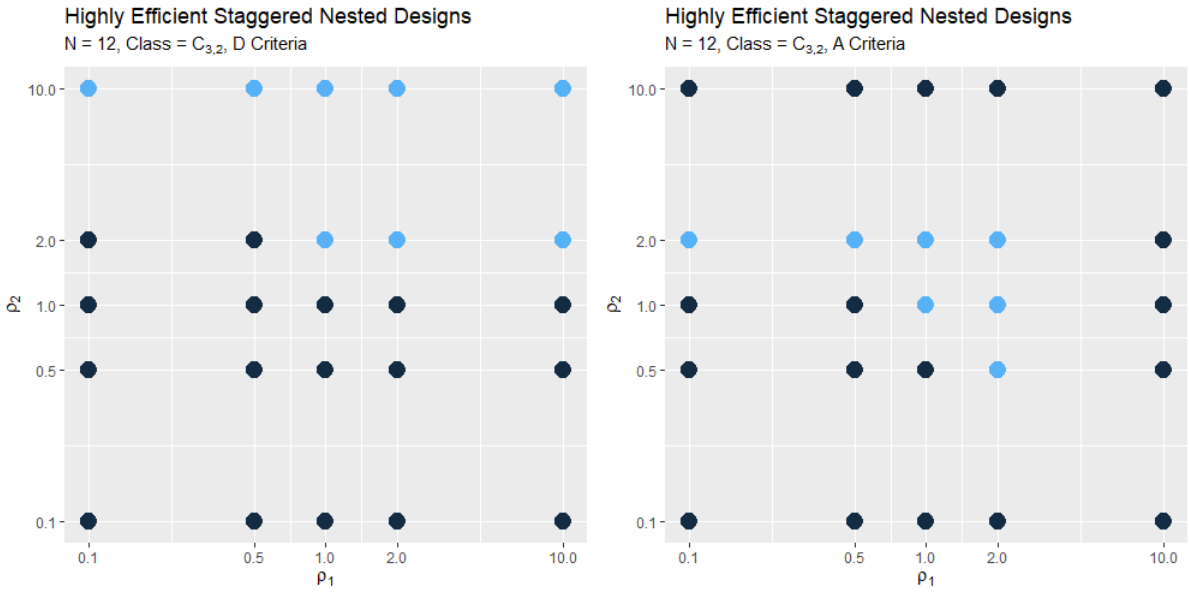

Figure 5.8: Given N=12 and designs are built from the $\mathcal{C}_{3,2}$ class, parameters that result in highly efficient staggered nested designs are highlighted in blue

We see a similar pattern emerge for designs of size $N = 24$ built from the class $\mathcal{C}_{3,2}$. One variation is that under the D criteria, the staggered nested design is only highly efficient when ρ_2

is much greater than ρ_1. See Figure 5.9 to see specific cases in which the staggered nested design is highly efficient under these parameters.

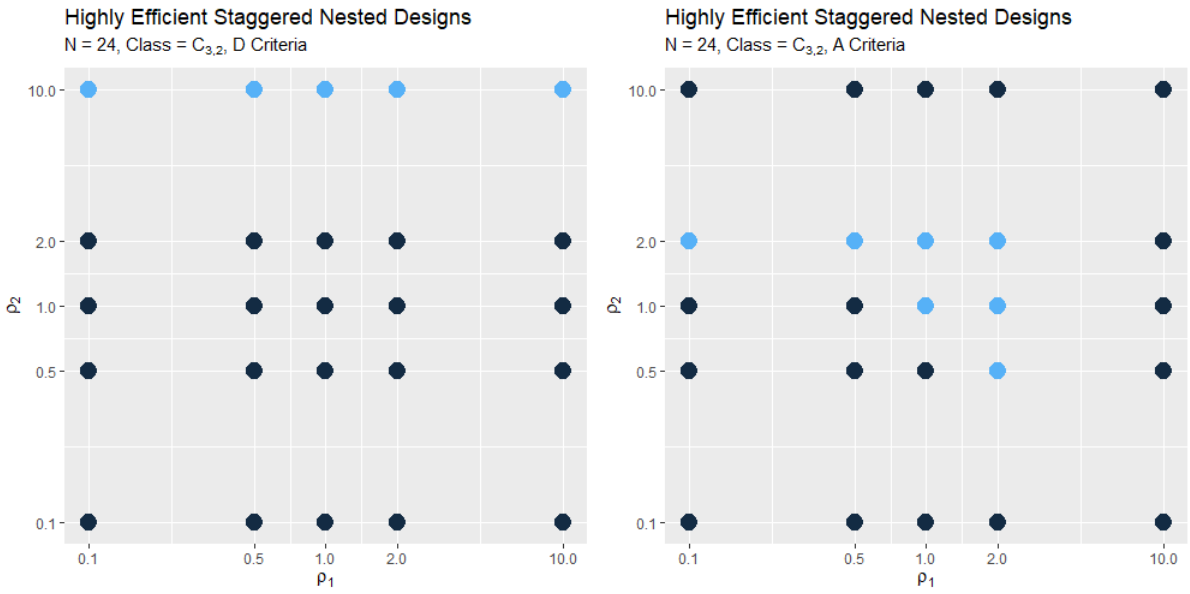

Figure 5.9: Given N=24 and designs are built from the $\mathcal{C}_{3,2}$ class, parameters that result in highly efficient staggered nested designs are highlighted in blue

When designs are built from the $\mathcal{C}_{3,3}$ class and $N = 12$, the staggered nested design is only highly efficient in two cases, both of which are under the A criteria: ($\rho_1 = 2$, $\rho_2 = 0.5$) and ($\rho_1 = 2$, $\rho_2 = 1$). The reason for this is that there are atoms within the $\mathcal{C}_{3,3}$ class that are not in $\mathcal{C}_{3,2}$ that more appropriately distribute degrees of freedom for this set of parameters. For example, the design built entirely from the atom in Figure 5.10, found within $\mathcal{C}_{3,3}$ and not $\mathcal{C}_{3,2}$, results in highly efficient designs for this set of parameters much more often than the atom represented in Figure 5.7.

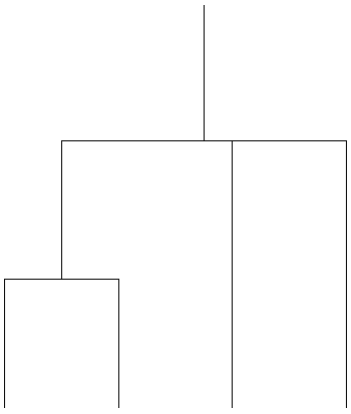

Figure 5.10: An atom from $\mathcal{C}_{3,3}$

5.7

Conclusion

The ODVC package has the necessary tools to explore interesting questions and design scenarios in the optimal design of experiments field for two-way nested random effects models. The `generate_two_way_designs` function returns a dataset of all designs of a specified size and class. Using Equation 2.18, these designs are scored on two optimality criteria. The dataset returned by this function makes identifying the optimal and other high performing designs simple. To visualize competing candidate designs, the user can call the `compare_designs_U` function. Once a design has been chosen, it can be visualized using the `plot_design_2` function. This allows the user to easily identify the structure of replicates nested within sub-groups nested within groups. These tools go beyond academic exploration of hypothetical scenarios and can be used for planning real life nested random effects experiments. See the vignettes included in Appendix B and the documentation for the ODVC package for more information. In the next Chapter, the research covered within this thesis will be summarized and further areas of research identified.

CHAPTER 6
REVIEW AND FURTHER RESEARCH

Although research had been done in optimal design of experiments for random effects models, the most important results of this research go back decades to a time when the computational resources to explore this problem were far fewer. The purpose of this thesis was to revive the exceptional work that had been done in this field and build an open-source R package that allows researchers to easily explore this problem. The ODVC package—accessed at `https://github.com/ryancbushman/ODVC`—allows researchers to do optimal design of experiments for both one-way and two-way nested random effects models. It includes tools that build comprehensive sets of experiments under certain design parameters as well as tools to score custom experiments based on whatever real-life limitations may exist for the experiment. The package also includes valuable visualization tools that aid in the analysis of competing experiment designs and the planning of the actual experiment.

A natural next step in the research is to expand the capability of the ODVC package to do optimal design for mixed effects models. In this setting, the information matrix would be a block diagonal matrix with two rows and two columns. One diagonal element would be the information matrix for the fixed effects while the second diagonal element would be the information matrix for the random effects [13]. It is supposed that the optimization of each information matrix could be done separately as the fixed effects matrix involves only the experiment settings of the fixed effects while the random effects matrix involves the allocation of replicates. For the fixed effects information matrix, one could look into using the classic Coordinate Exchange optimization algorithm or a less greedy algorithm such as Particle swarm or Differential Evolution. The optimization of the random effects information matrix would not involve an algorithm, but generating all experiments based on the design parameters, scoring them under a criterion, and selecting the best performing design based on the real-life experiment limitations. Although the expansion of this package is well envisioned, there are many interesting questions that can be explored once the tools exist.

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APPENDICES

APPENDIX A: OPTIMAL DESIGNS FROM CHAPTER 5 ANALYSES

This appendix contains Figures of designs that were optimal for at least one set of parameters explored in the analyses contained in Chapter 5. Using the Tables in Chapter 5 and the Figures in this appendix, one can identify the optimal design for the parameters in question.

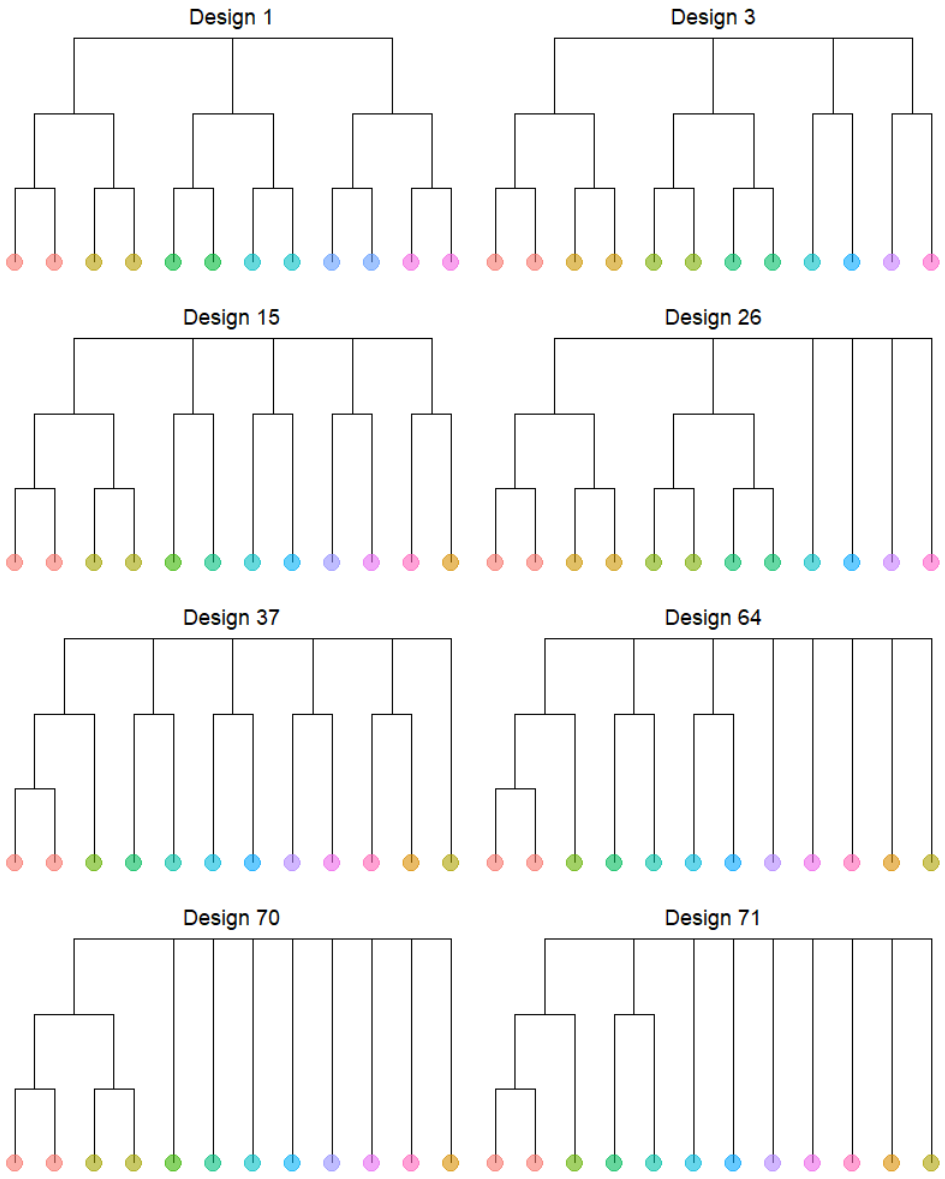


Figure 6.1: Designs of size $N = 12$ from $\mathcal{C}_{3,2}$ that were found to be optimal for at least one combination of the prespecified values of ρ_1 and ρ_2.

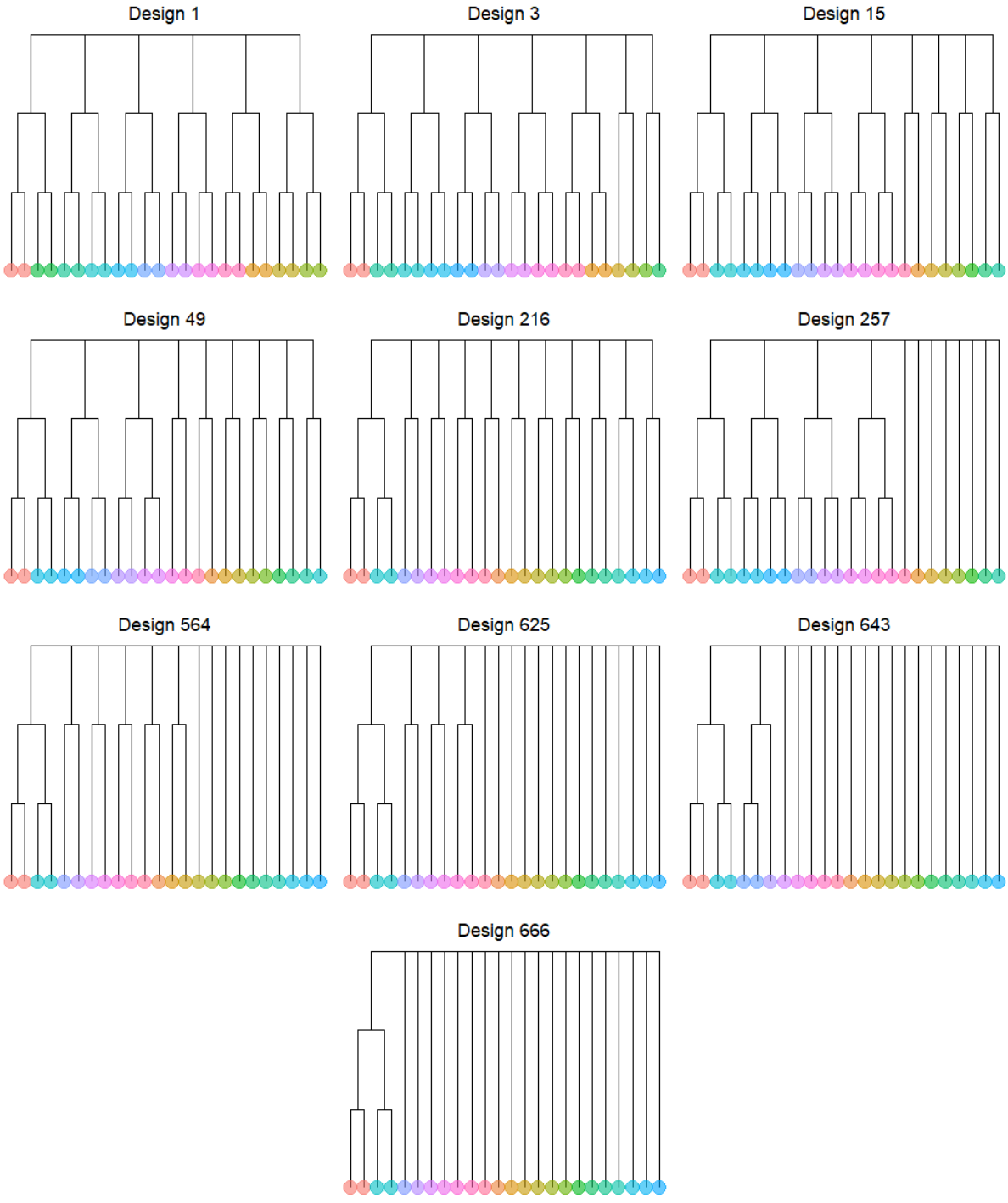


Figure 6.2: Designs of size $N = 24$ from $\mathcal{C}_{3,2}$ that were found to be optimal for at least one combination of the prespecified values of ρ_1 and ρ_2.

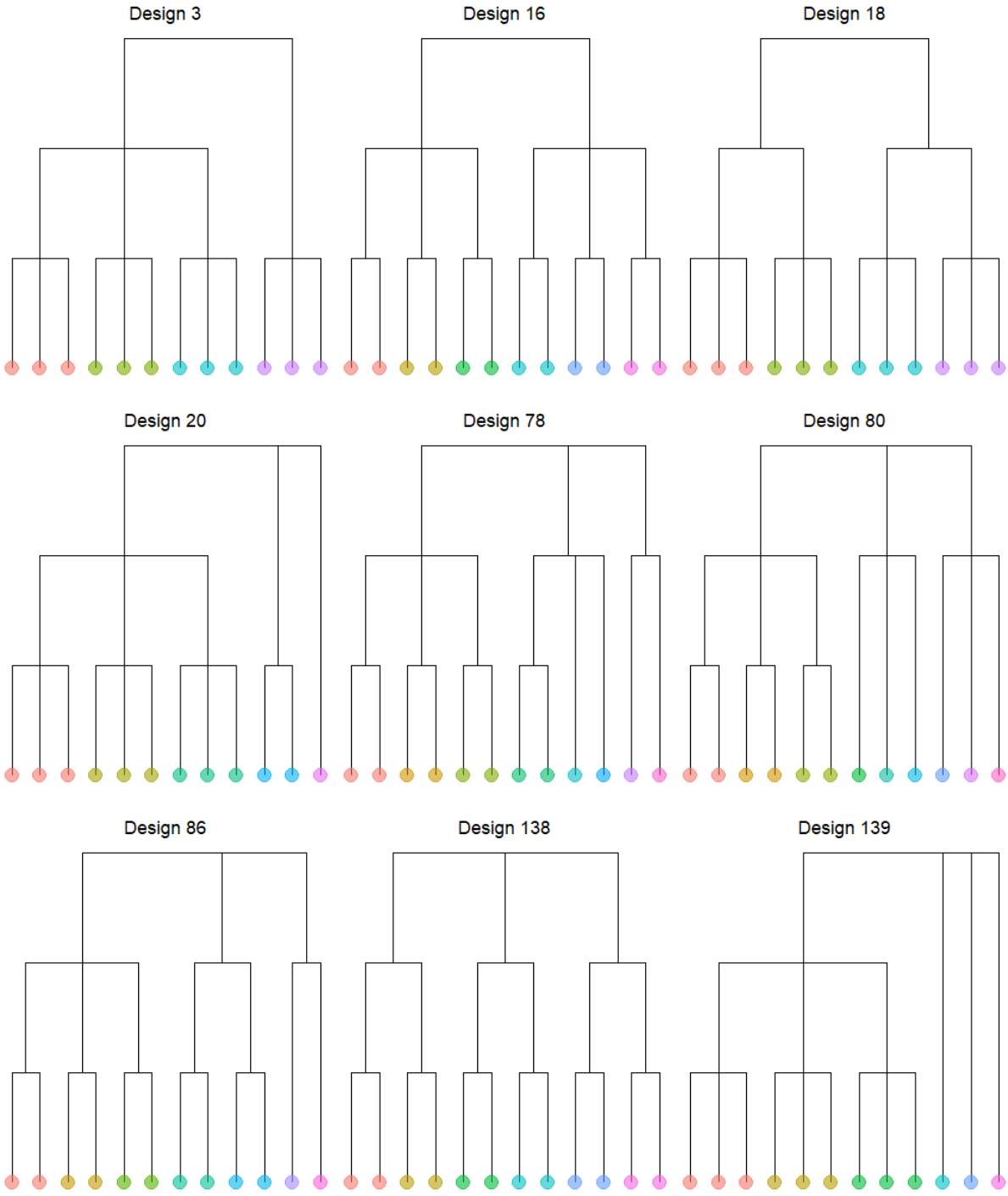


Figure 6.3: Designs of size $N = 12$ from $\mathcal{C}_{3,3}$ that were found to be optimal for at least one combination of the prespecified values of ρ_1 and ρ_2.: Part 1

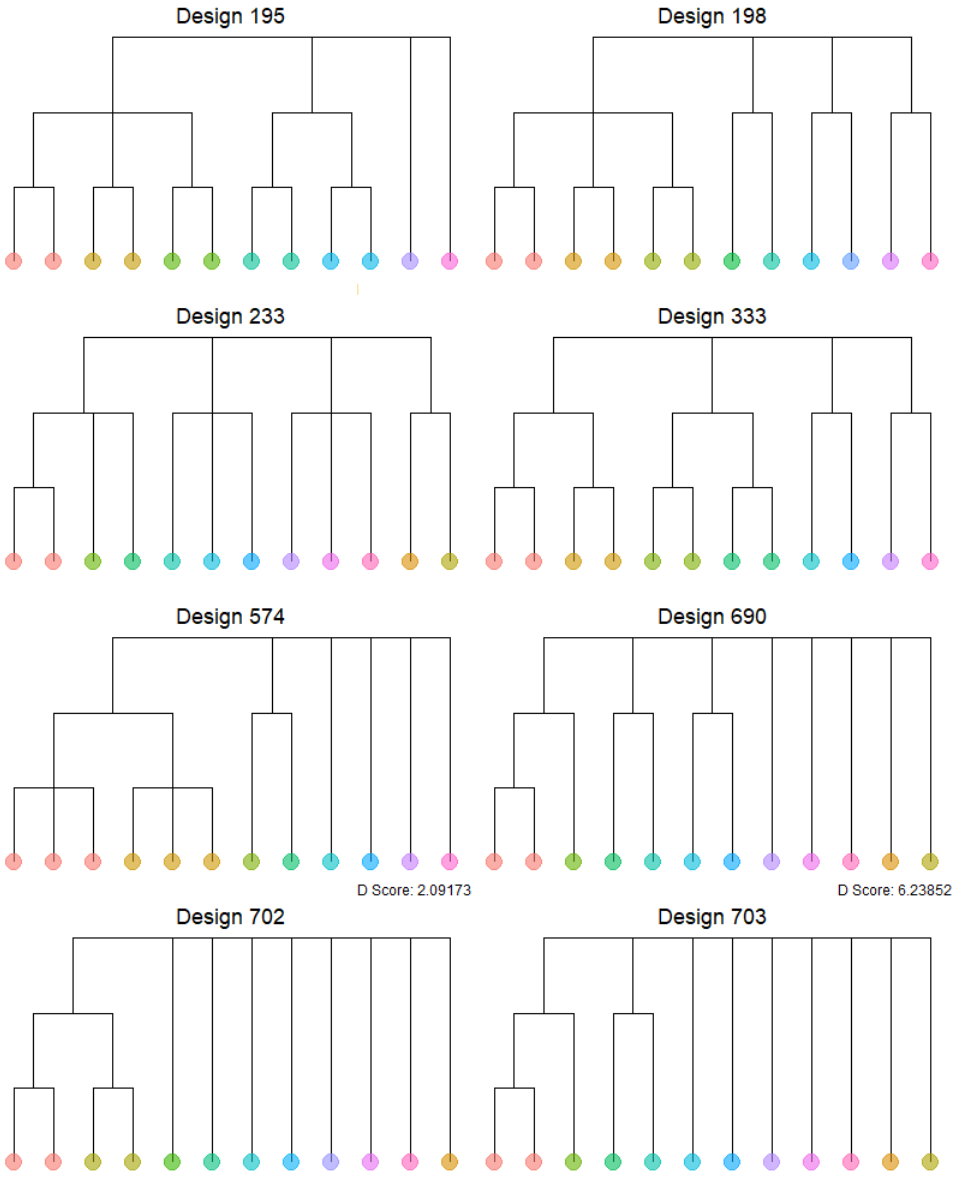


Figure 6.4: Designs of size $N = 12$ from $\mathcal{C}_{3,3}$ that were found to be optimal for at least one combination of the prespecified values of ρ_1 and ρ_2.: Part 2

APPENDIX B: ODVC VIGNETTES

This appendix contains the two rendered R Markdown vignettes that are included in the ODVC package. These vignettes demonstrate for the user how the tools in the ODVC package can be used to do optimal design of experiments for both one-way and two-way random effects models.

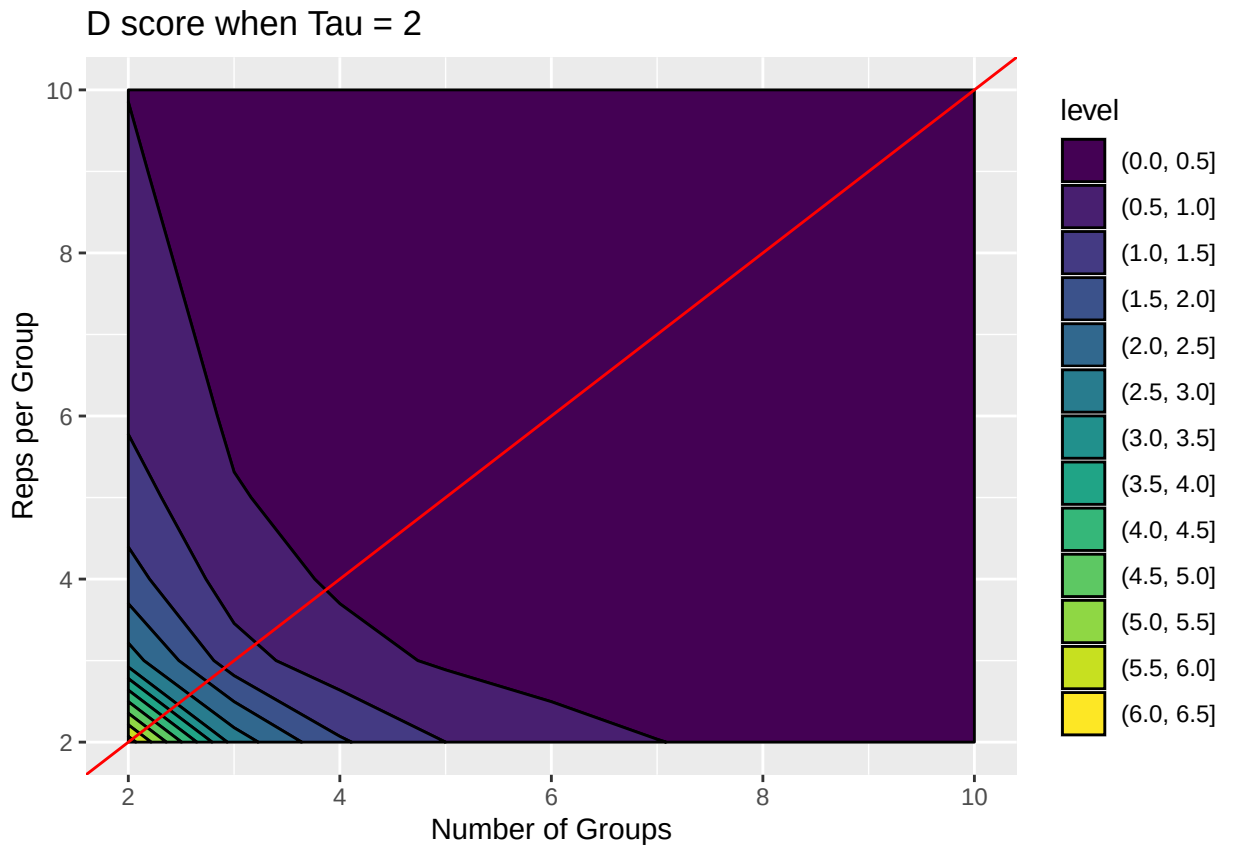
Tools For One-Way Models

```
library(ODVC)
library(ggplot2)
```

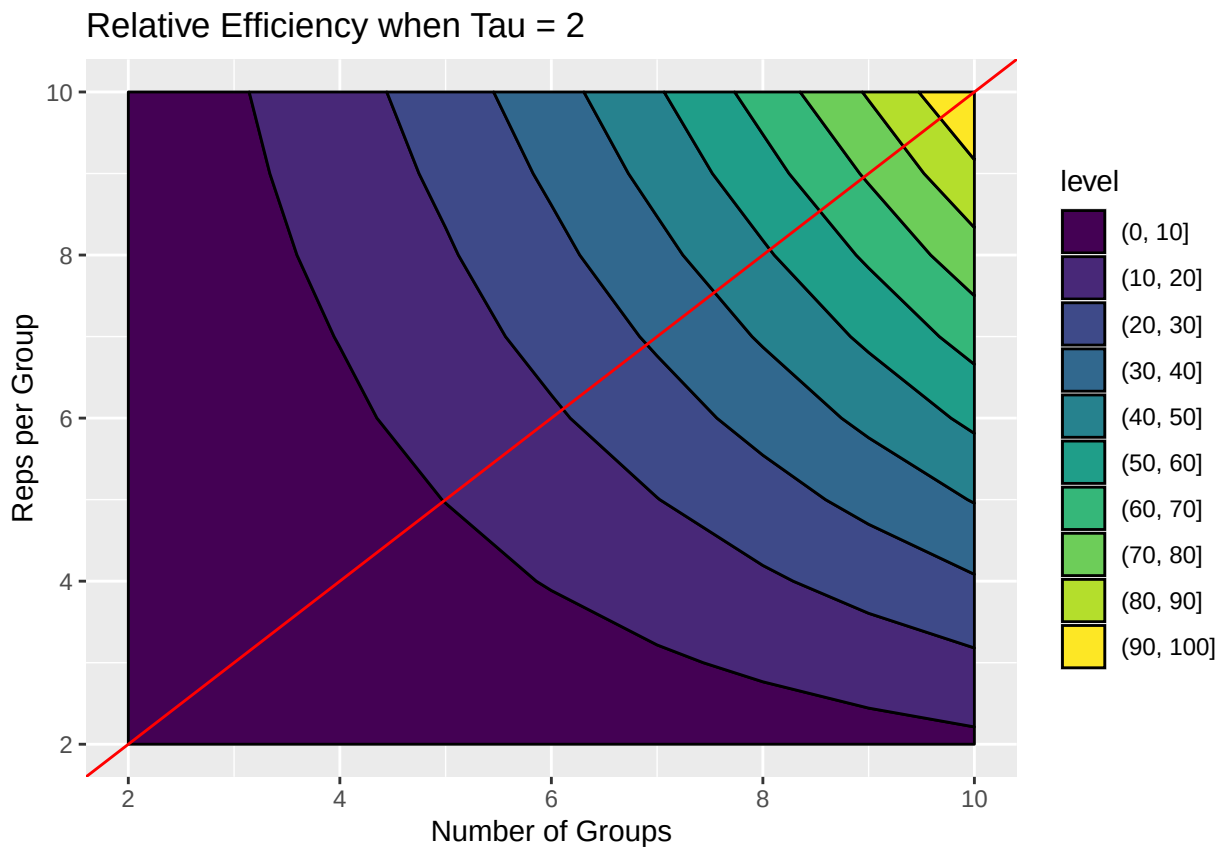
If a user would like to explore a wide variety of balanced one-way nested random effects designs with many different parameter settings, they can use contour_designs_B function.

```
contour_plots <- contour_designs_B(ngroups = c(2, 10), nreps = c(2, 10),
                                   taus = 2)
```

```
contour_plots[[1]][[4]]
```




```
contour_plots[[2]][[4]]
```



Once the user narrows down what parameter settings they would like to explore, they can use the generate_designs_B to generate balanced designs.

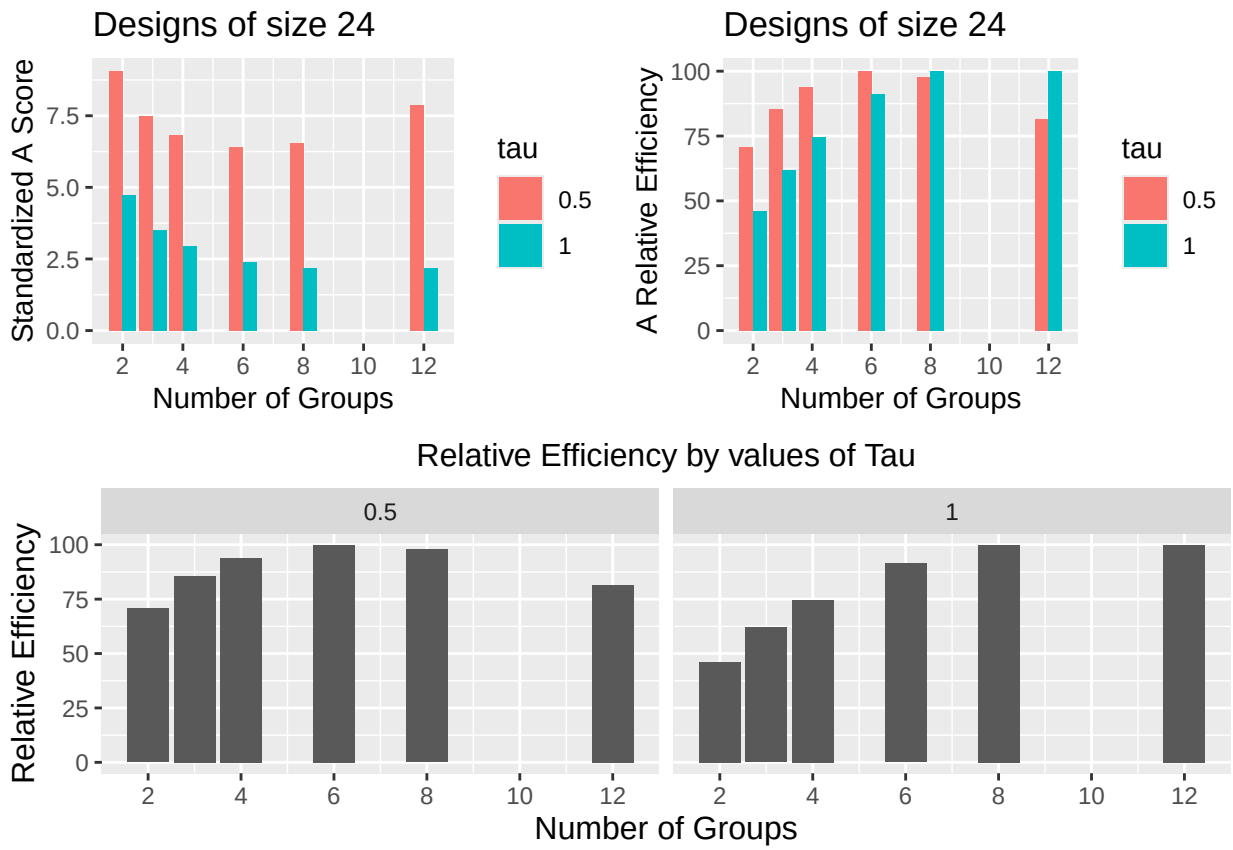
```
candidates_B <- generate_designs_B(ngroups = c(2, 3, 4, 6, 8, 12),
                                   nreps = c(2, 3, 4, 6, 8, 12),
                                   taus = c(0.5, 1))
head(candidates_B)
#>   N a n tau   A_Score   D_Score Relative.A.Efficiency Relative.D.Efficiency
#> 1 4 2 2 0.5 2.2500000 1.0000000              3.198653             0.08592873
#> 2 4 2 2   1 3.5000000 2.2500000              2.056277             0.03819055
#> 3 6 2 3 0.5 1.2500000 0.3472222              5.757576             0.24747475
#> 4 6 2 3   1 2.3333333 0.8888889              3.084416             0.09666982
#> 5 8 2 4 0.5 0.9166667 0.1875000              7.851240             0.45828657
#> 6 8 2 4   1 1.9166667 0.5208333              3.754941             0.16498316
```

The subset_designs_B function can be used to select only the designs of a particular size.

```
candidates_B_N24 <- subset_designs_B(data = candidates_B, N = 24)
head(candidates_B_N24)
#>     N a  n tau   A_Score    D_Score Relative.A.Efficiency Relative.D.Efficiency
#> 11 24 2 12 0.5 0.4318182 0.03093434              70.76023              67.34694
#> 12 24 2 12   1 1.2651515 0.10669192              46.10778              52.07101
#> 21 24 3  8 0.5 0.3571429 0.02480159              85.55556              84.00000
#> 22 24 3  8   1 0.9404762 0.08035714              62.02532              69.13580
#> 31 24 4  6 0.5 0.3250000 0.02222222              94.01709              93.75000
#> 32 24 4  6   1 0.7833333 0.06805556              74.46809              81.63265
```

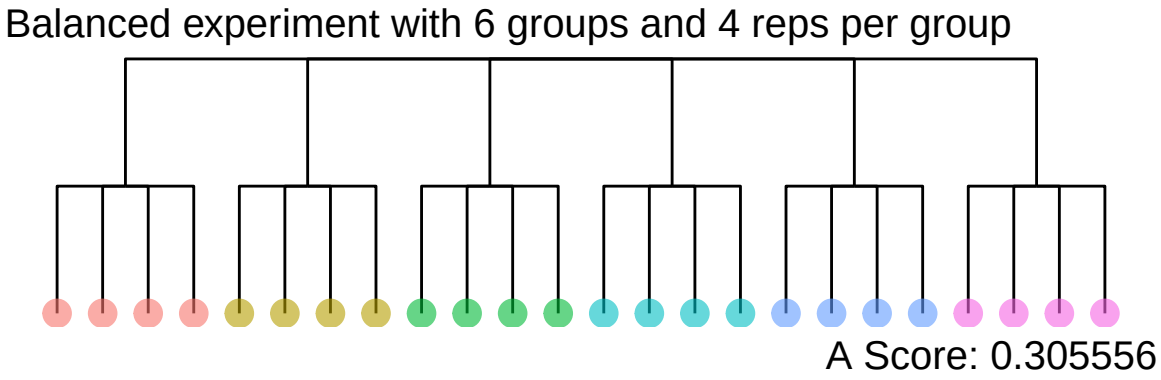
The user can then use the compare_designs_B function to create a dashboard that will help them to choose the optimal design.

```
compare_designs_B(designs = candidates_B_N24, criteria = "A")
```



From the dashboard, the user can see that when $\sigma_A^2 = 0.5$, the best design when N=24 under the A criteria is the one that has 6 groups. The user can now use the plot_design function to visualize the design.

```
plot_design(n = rep(4, 6), a = 6, sig_a_sq = 0.5, error_sq = 1, criteria = "A")
```



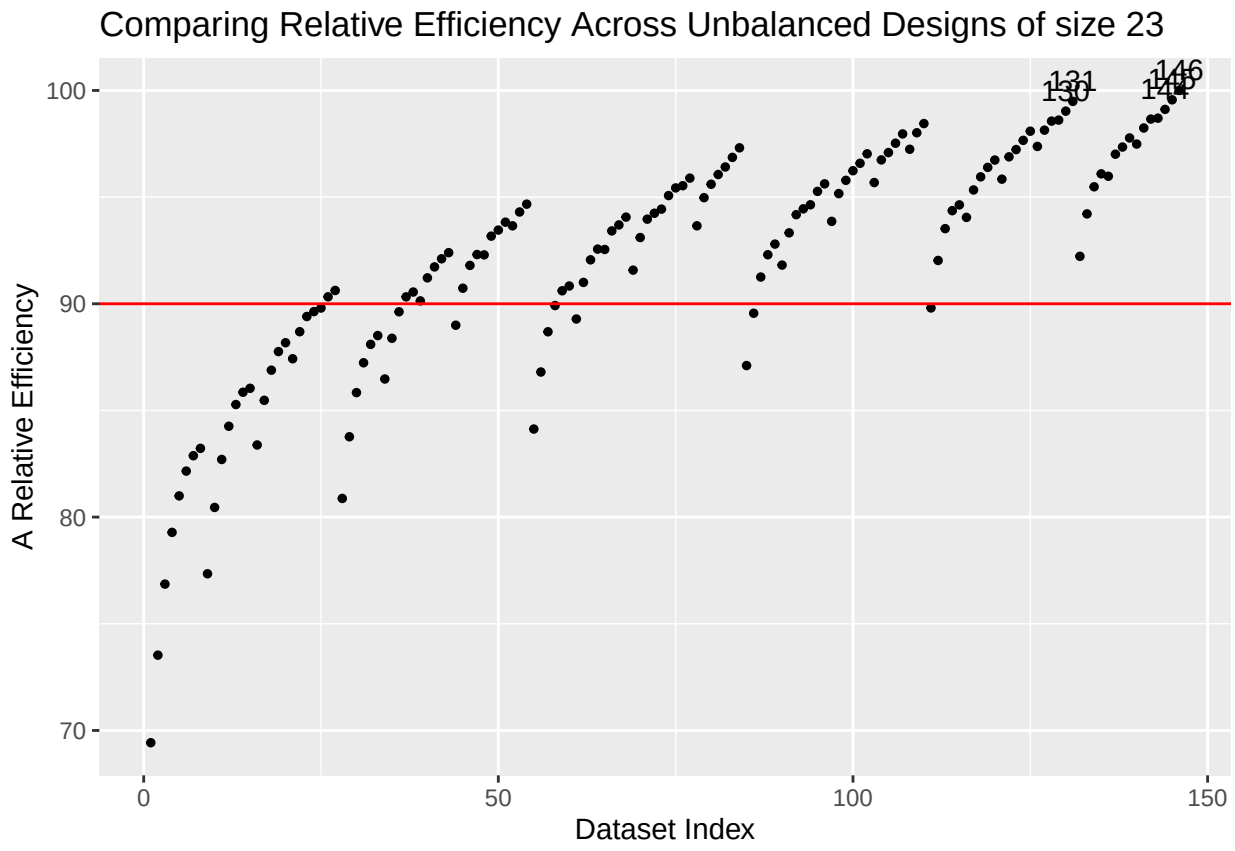
If the user would like to explore unbalanced designs, they can use the generate_designs_U function.

```
options(width = 60)
candidates_U <- generate_designs_U(N = 23, a = 8, sig_a_sq = 0.5, error_sq = 1)

head(candidates_U)
#>    N a              n_i sig_a_sq   A_Score    D_Score
#> 1 23 8 16 1 1 1 1 1 1 1      0.5 0.4750000 0.03894231
#> 2 23 8 15 2 1 1 1 1 1 1      0.5 0.4484886 0.03629817
#> 3 23 8 14 3 1 1 1 1 1 1      0.5 0.4290559 0.03430875
#> 4 23 8 13 4 1 1 1 1 1 1      0.5 0.4159344 0.03295255
#> 5 23 8 12 5 1 1 1 1 1 1      0.5 0.4071491 0.03204010
#> 6 23 8 11 6 1 1 1 1 1 1      0.5 0.4013934 0.03144064
#>   Relative.A.Efficiency Relative.D.Efficiency
#> 1              69.42512              61.69873
#> 2              73.52903              66.19317
#> 3              76.85929              70.03144
#> 4              79.28398              72.91366
#> 5              80.99474              74.99011
#> 6              82.15615              76.41991
```

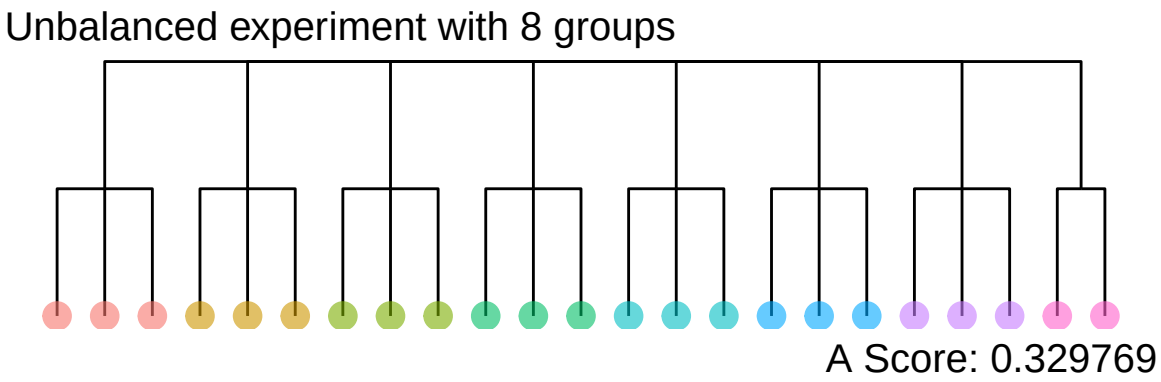
To compare the performance of these designs they can use the compare_designs_U function. This generates a scatter plot of relative efficiency and index within the design dataframe. The user can also set the top_5 argument equal to TRUE to label only the top 5 performing designs.

```
compare_designs_U(data = candidates_U, criteria = "A", top_5 = TRUE)
```



From the plot, it is evident that the best design is the one with index 146 from the dataframe. By referencing this row in the dataframe, the user can use the plot_design function to visualize this optimal design.

```
plot_design(n = c(rep(3, 7), 2), a = 8, sig_a_sq = 0.5, error_sq = 1,
            criteria = "A")
```



In the optimal design of experiments framework, the goal is to optimize the model information matrix. The inverse of the information matrix is the covariance matrix for the maximum likelihood estimators. By maximizing the information of an experiment on some optimality criteria, one simultaneously minimizes the variance of the maximum likelihood estimators. The information matrix can be scored using optimality criteria such as the D criteria (the determinant) or the A criteria (the trace). The tools of the ODVC package define the optimal design as the design the minimizes the optimality criteria. In a random-effects model, the information matrix is a function of the experiment's sample sizes and the values of the variance components. The user can use the general_variance_2VC function to generate the covariance matrix of the maximum likelihood estimators (the object being optimized) for a particular experiment.

```
optimal_design_inv_info_matrix <- general_variance_2VC(N = 23, n = c(rep(3, 7), 2),
                                                       a = 8, sig_a_sq = 0.5,
                                                       error_sq = 1)

optimal_design_inv_info_matrix
#>              [,1]        [,2]
#> [1,]  0.13310908 -0.04637194
#> [2,] -0.04637194  0.19666026
```

The user can then use either the A_crit or D_crit function to report a score.

```
A_crit(optimal_design_inv_info_matrix)
#> [1] 0.3297693
D_crit(optimal_design_inv_info_matrix)
#> [1] 0.02402691
```

Tools For Two-Way Models

```
library(ODVC)
```

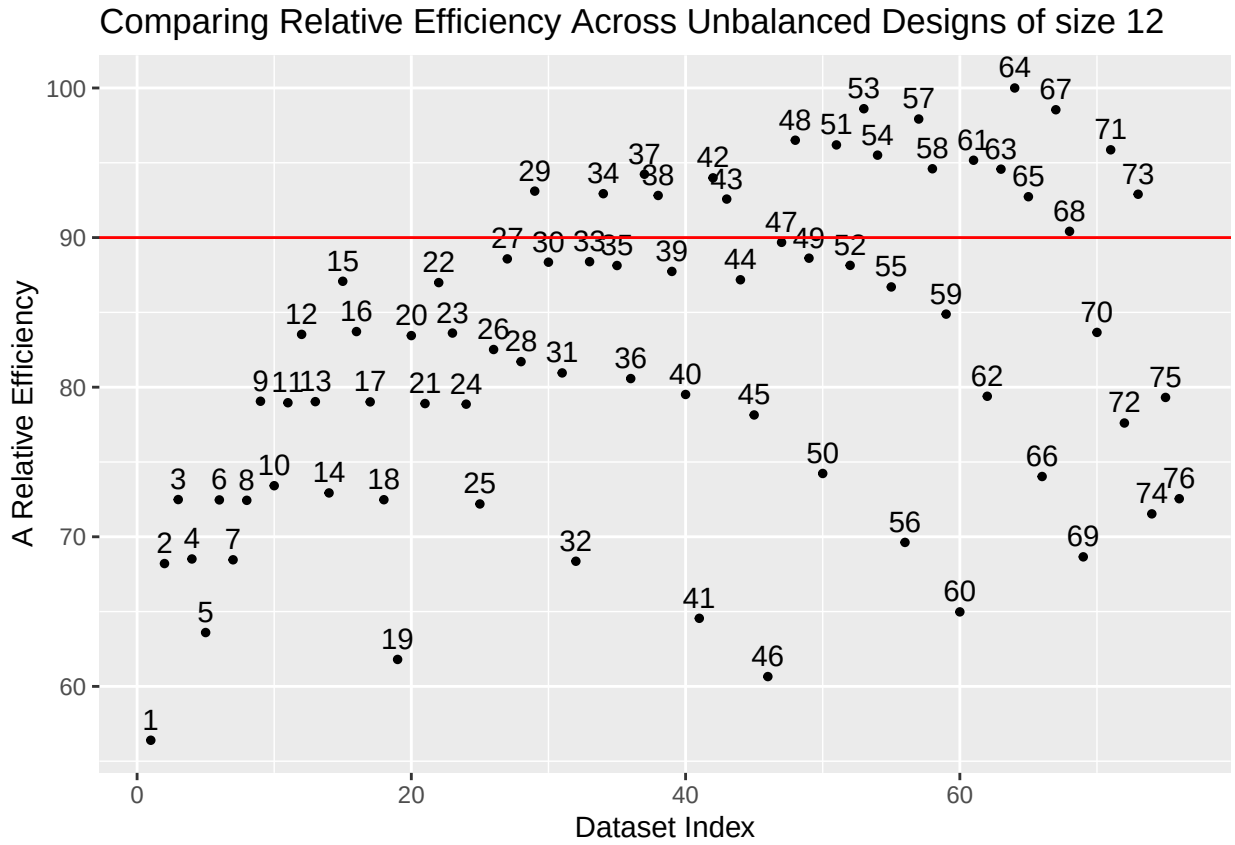
Optimal design of experiments for a random-effects model is a combinatorial problem in nature. The reason being is that the object being optimized, the inverse information matrix, is a function of the sample sizes of the experiment and the values of the variance components. When searching the space of possible designs, one must generate all designs of size N and score the inverse information matrix of each design on some optimality criteria. When exploring two-way nested models, the amount of possible designs of size N grows exceptionally fast as N increases. Two mitigate this, the ODVC generates all designs of a chosen N from one of two classes, $\mathcal{C}_{3,2}$ and $\mathcal{C}_{3,3}$. The first subscript indicates the number of variance components. The second subscript indicates the maximum number of subgroups per group and the maximum number of replicates per subgroup.

The user can use the generate_two_way_designs function to generate all designs of size N from class s, with variance components σ_A^2, σ_B^2, and σ^2.

```
candidates <- generate_two_way_designs(N = 12, s = 2, sig_a_sq = 10,
                                       sig_b_sq = 2, error_sq = 1)
```

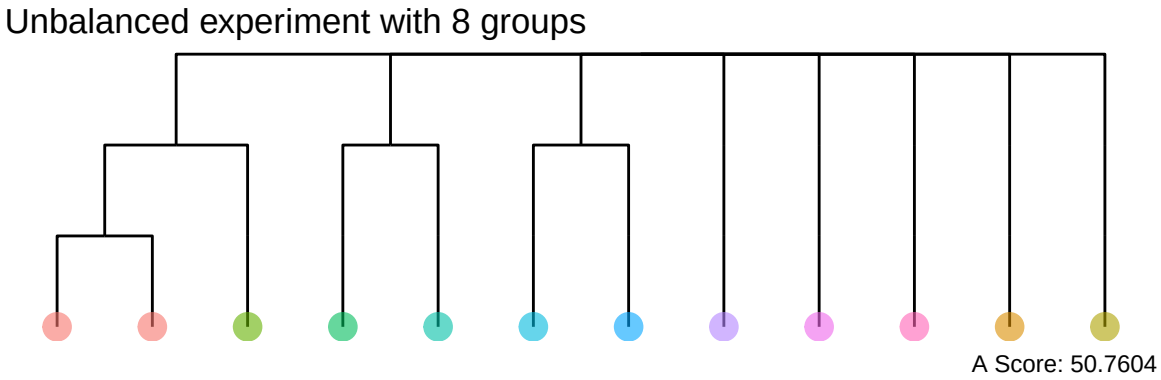
Once the dataframe of designs is generated, the user can call the compare_designs_U function to compare design performance.

```
compare_designs_U(data = candidates, criteria = "A")
```



The plot indicates that design 64 from the dataframe is the optimal design. By referencing the dataframe, the user can call the plot_design_2 function to visualize the design.

```
plot_design_2(a = 8,
              b_i = c(2, 2, 2, 1, 1, 1, 1, 1),
              n_ij = c(2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1),
              n_i_dot = c(3, 2, 2, 1, 1, 1, 1, 1),
              sig_a_sq = 10,
              sig_b_sq = 2,
              error_sq = 1,
              balanced = FALSE,
              criteria = "A")
```



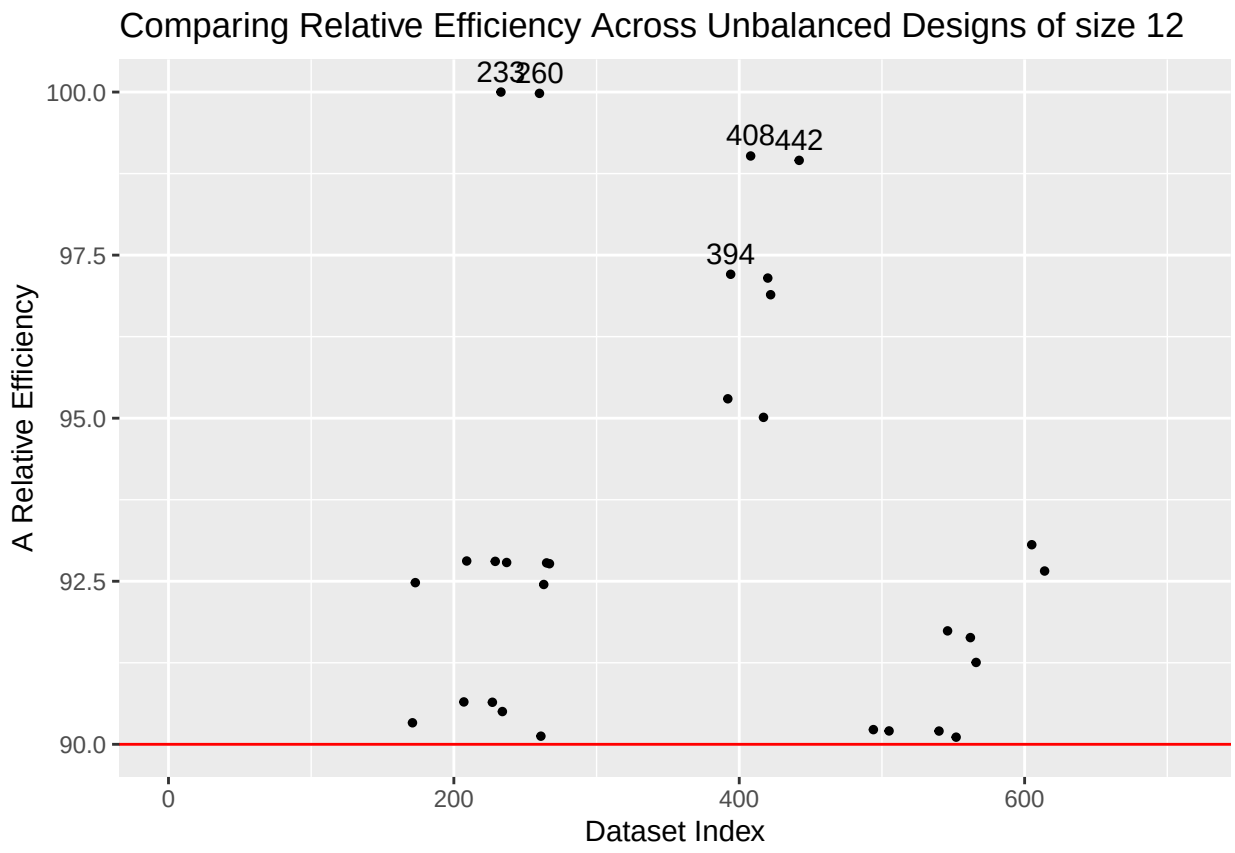
We will now walk through a different design scenario and but generate designs from $\mathcal{C}_{3,3}$ rather than $\mathcal{C}_{3,2}$.

Note that this takes much longer to do because the number of possible designs is much greater.

```
candidates2 <- generate_two_way_designs(N = 12, s = 3, sig_a_sq = 10,
                                        sig_b_sq = 10, error_sq = 1)
```

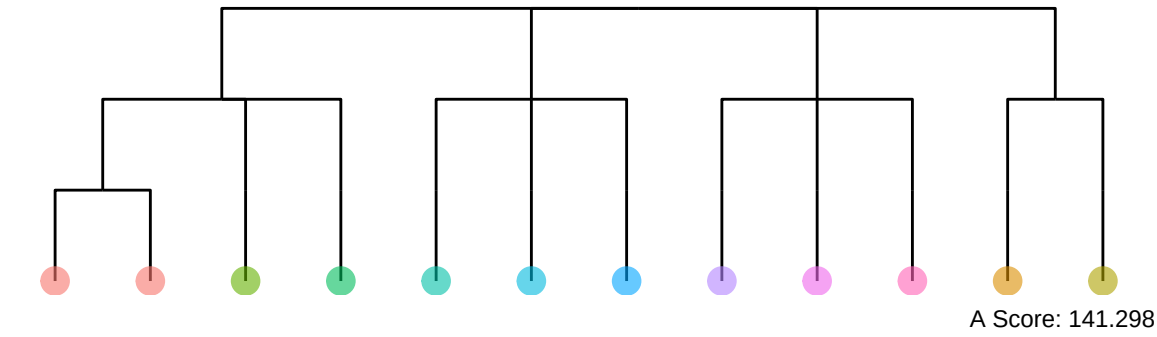
Once the dataframe of designs is generated, the user can call the compare_designs_U function to compare design performance. They can also set the top_5 argument equal to TRUE to label only the top 5 performing designs.

```
design_performance <- compare_designs_U(data = candidates2, criteria = "A",
                                        top_5 = TRUE)
design_performance + ggplot2::ylim(90, 100)
```



The plot indicates that design 233 from the dataframe is the optimal design. By referencing the dataframe, the user can provide the necessary information to call the plot_design_2 function and visualize the design.

```
plot_design_2(a = 4,
              b_i = c(3, 3, 3, 2),
              n_ij = c(2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1),
              n_i_dot = c(4, 3, 3, 2),
              sig_a_sq = 10,
              sig_b_sq = 10,
              error_sq = 1,
              balanced = FALSE,
              criteria = "A")
```



The tools in the ODVC package score the designs for the user. If the user would like to generate the actual matrix that is being optimized themselves, they can call the general_variance_3VC function.

```
optimal_design_inv_info_matrix <- general_variance_3VC(N = 12,
                                                       n_i_dot = c(4, 3, 3, 2),
                                                       n_ij = c(2, 1, 1, 1, 1, 1, 1,
                                                                1, 1, 1, 1),
                                                       sig_a_sq = 10,
                                                       sig_b_sq = 10, error_sq = 1)
optimal_design_inv_info_matrix
#>                [,1]       [,2]         [,3]
#> [1,] 103.293304049 -12.568802 -0.005530026
#> [2,] -12.568801683  36.007330 -1.897203980
#> [3,]  -0.005530026  -1.897204  1.997775399
```

They can then score the design using either the A_crit or D_crit function.

```
A_crit(optimal_design_inv_info_matrix)
#> [1] 141.2984
D_crit(optimal_design_inv_info_matrix)
#> [1] 6742.703
```