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Bootstrap Analysis Double-Independent Programming: Issues and Solutions.

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ABSTRACT

Bootstrap analysis is a valuable, iterative, statistical analysis tool useful when the distribution of an analysis variable is unknown, and likely non-normal and/or non-symmetrical. This family of techniques is garnering attention in the pharmaceutical industry with the development of faster and more powerful computers. The downside of such iterative analysis emerges when the final bootstrap results are to be included in a submission to regulatory authorities. In order to ensure that the bootstrap results are validated appropriately, double-independent programming is the preferred method. Unfortunately, bootstrap ADaM datasets used for these planned analyses are large, complex, and challenging to produce. They also cause extended processing times reading or writing to storage. Double-programming only magnifies these issues. This paper will present a case study of bootstrap analysis with a PRO efficacy endpoint to illustrate the issues and solutions that arise during double-independent programming validation.

INTRODUCTION

Bootstrapping is an umbrella term that covers a set of simulation-based methods using re-sampling as a way of approximating population distribution from a sample. Double-independent programming of the bootstrap-t technique will be presented. This technique is useful when a researcher is interested in knowing whether the arithmetic mean difference between two groups is significant, but the usual statistical assumptions are not likely to be met. With this technique, it is possible to compare two means and decide whether they are significantly different. This method is particularly suited to the analysis of Health Economics or Patient Reported Outcomes parameters. In this work, we will illustrate the method using data coming from the WPS questionnaire.

The Work Productivity Survey (WPS) is a patient reported questionnaire measuring the impact of Rheumatoid Arthritis on the daily life of patients, both at work and at home (Osterhaus, Richard, & Purcaru, 2008). This questionnaire features eight questions; the patients' answers to each of these questions are considered outcomes. The answers for the WPS questions are usually far from normally distributed. This precludes the use of standard statistical measures based on distribution assumption such as a t-test.

Bootstrap analyses are often conducted using the boot macro provided on the SAS web site. This macro is very efficient and versatile but presents some inconveniences in the framework of double-programming. One limitation of this macro is that it is not validated by the SAS institute and is only provided by online SAS Support.
Another complication is that each re-run of the program will use a different re-sampling (the SEED parameter is always different); this prevents any kind of validation by double-programming as the final results are likely to differ between two different runs of the program. It also means that the final results are likely to change with each re-run. A third issue is that the bootstrap macro by SAS does not integrate a variance stabilization module. This is an issue because previous analysis on WPS data has shown that bootstrap analysis without variance stabilization was sometimes heavily biased (Osterhaus, Richard, & Purcaru, 2009).

Double-independent programming is a quality control method widely used in the pharmaceutical industry. This method reduces the occurrences of programming errors as well as the uncertainty linked to the interpretation of specifications. Reconciling differences is an iterative process and may be time-consuming depending on the complexity of the output to control. The author will discuss the unique challenges emerging from double-programming a bootstrap analysis.

This paper presents an example for the bootstrap-*t* comparison between two treatment groups: a first group of patients taking an active drug (Active) and a second group of patients taking a placebo drug (Placebo). This example presents the case for one question, one time point, and one comparison. It uses an alpha level of $\alpha=0.05$ and B, the number of replication is 10000. In a more realistic setting, it is likely that this bootstrap analysis would entail many more questions, time points, and comparisons. As a reference, this example can also be used as a companion to the Barber and Thompson (2000) paper.

Following this introduction, the analysis presented is organized into three chapters. The first chapter demonstrates how to implement re-sampling. The second chapter describes how to compute the statistics for each re-sample. And finally, the third chapter explains how to derive the final output of the bootstrap-t: p-value and confidence interval. Each of these chapters discusses both the issues encountered as well as solutions provided.

1-RE-SAMPLING MODULE

The core of the bootstrap technique is to re-sample an observed sample a large number of times in order to estimate the shape of the distribution of a statistical estimator under the null hypothesis. This can be done by re-sampling randomly directly from the sample a large number of times. Although there are many different re-sampling techniques, the present example uses a stratified and balanced re-sampling with replacement. In this type of re-sampling, the re-sampling is conducted independently in each sub-group (e.g., Active Drug and Placebo). The rationale behind the stratification is to reduce the bias potentially caused by the fact that the distributions of each of these experimental groups are different. Because of the replacement aspect, one particular patient may appear several times in one sample and not at all in another sample. In order to control for a bias in patient selection, each of the patients will appear an equal number of times. For instance, if 10000 random samples are created, Patient 1 will appear 10000 times.

Although this type of sampling appears complicated, it is relatively simple to implement. Unfortunately, although SAS (r and 9.1.3) provides PROC SURVEY SELECT, a ready-made procedure specialized to efficiently implement many re-sampling techniques, this procedure does not allow for balanced sampling. However, it can still be used in conjunction with other datasteps to fulfill this criterion. The following section describes how to implement such stratified balanced sampling.

1.1 DESCRIPTION OF THE SAMPLING ALGORITHM

The description of the algorithm of balanced stratified sampling used in this paper can be found in Gleason (1988). In the first step, duplicate and concatenate the observed data the same number of times as the number of bootstrap replications. Randomly shuffle this replication. Then slice this shuffled vector into subparts that have the same size as the observed group. Figure 1 illustrates how this algorithm works.

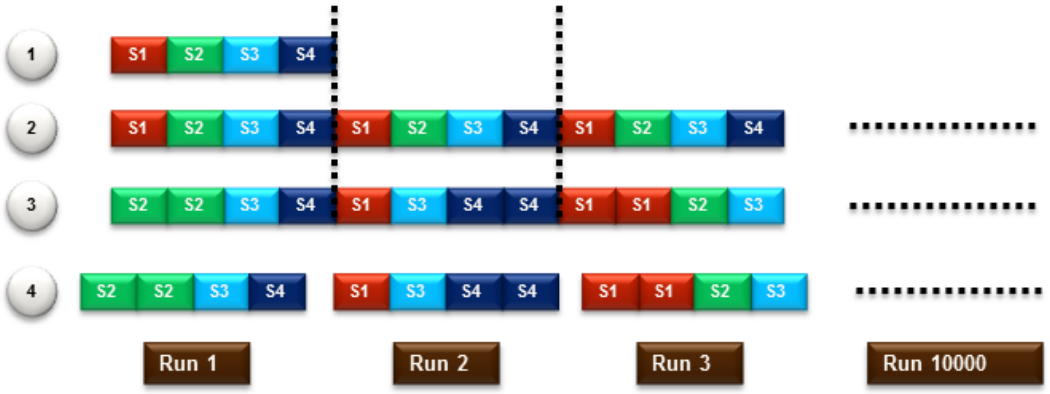


Figure 1: Illustration of the balanced sampling algorithm. Step 1 represents an observed sample for one group made up of four patients (S1, S2, S3 and S4). In Step 2, this observed sample is replicated the same number of times as planned bootstrap runs. In Step 3, the vector representing all of the replications is randomly permuted. Each of the slices pictured in Step 4 represents one re-sampling.

The following sections describe the SAS implementation of the Gleason (1988) algorithm as presented by Figure 1.

In order to replicate the original observed data the same number of times as bootstrap replications, it is possible to use PROC SURVEYSELECT. Note that in this paper; in contrast with the common use of this procedure, no random sampling occurs during this step.

```
PROC SURVEYSELECT NOPRINT DATA=indata OUT=sampling01
              SEED=123 /*Seed of no importance here*/
              METHOD=SRS
              SAMPRATE=1
              REP=10000
;

RUN;
```

This bit of code replicates the dataset `indata` 10000 times. The dataset `indata` corresponds to Step 1 in Figure1 while the result of this replication corresponds to Step 2 in Figure 1. PROCSURVEY allows for an efficient and fast creation of this large vector. An additional benefit of PROCSURVEY is that it produces a very useful variable called "Replicate". This variable labels each of the replications created by this procedure. This variable will be used to implement the "slicing" (See Step 3 in Figure 1).

Once the large vector has been created, it needs to be randomly permuted (as described at Step 3 in Figure 1). In order to do so, a simple datastep with a SEED statement will suffice. One way to implement this shuffling is as follows:

```
%LET seed=42;

DATA sampling02;
SET sampling01;
rank=ranuni(&seed);
RUN;
```

The random variable `rank` is then used as a sort key to implement the shuffling:

```
PROC SORT DATA=sampling02;
BY rank;
RUN;
```

The next step implements the "slicing" using a MERGE statement. The idea is simply to merge together the original dataset containing the original replicated vector and the `replicate` variable (sampling01, with replicate going from 1 to 10000 and coding for the bootstrap re-sample), and the corresponding randomly-sorted dataset (sampling02). The implicit MERGE key in this case is the observation rank.

The need for a merge key is unnecessary in this process for two reasons. First, the datasets exhibit exactly the same number of observations. Second, the datasets already feature the desired order. Note the use of OPTIONS MERGENOBY = NOWARN to prevent MERGE from displaying the warning that the user is attempting to merge without a key. Of course, It is recommended to reinstate this warning once the merge is completed (OPTIONS MERGENOBY = WARN). Obviously, this type of merge should be used with caution.

A beneficial outcome of this method is the avoidance of extraneous PROC SORT or DO loops. Keep in mind that because ADaM datasets store data in a vertical structure, the number of observations can be quite large. This has a significant impact in terms of sorting time performance and/or loops.

```
OPTIONS MERGENOBY=NOWARN; /*Danger Will Robinson*/
DATA sampling03;
MERGE  sampling01 (KEEP = replicate)
       sampling02 (KEEP = usubjid boottrt aval);

RUN;
OPTIONS MERGENOBY=WARN; /*Everything is safe again*/
```

The next PROC SORT simply shapes the data allowing SAS to directly use replicate as a by group factor in the following statistical computations:

```
PROC SORT DATA=sampling03;
BY replicate usubjid;
RUN;
```

1.3 ISSUES WITH DOUBLE-PROGRAMMING THE RE-SAMPLING

Programmers are faced with three main problems in the context of double programming the necessary sampling algorithm. The first is the random aspect of sampling. The second is to produce a balanced sample. Finally, a third issue results from the large amount of data generated in this step. It is important that both the development programmer and the validation programmer agree on a detailed description of the program structure. Also, an agreement on the order in which the operations are to be performed will facilitate the validation process.

It is critical that both the development side and the validation side produce the exact same re-sampling of the data. If this condition is not respected, there will be differences in the final bootstrap results. The program described in the previous section provides a simple example of how to have a controlled randomness that is the same in both programs. This program also addresses the need for balance by following the algorithm proposed by Gleason.

The remaining issue involves the process rather than programming. Validating this type of analysis using double-programming is difficult because of the discrepancy between the huge amount of data created by the intermediary steps, and the small size of the final results. Indeed, the re-sampling can create millions of observations. The mechanics of the bootstrap reduces this large number of data into a very nimble statistical output: a p-value and a confidence interval. The issue here is twofold: when a difference is found in the final results, it could originate from these millions of observations. This means that the re-sampling intermediary datasets need to be kept to provide a trace of how the data was re-sampled. The second aspect of this issue originates from the first one: keeping a trace of all the intermediary datasets will quickly become difficult to manage in the framework of a clinical study folder structure.

For instance, in the presented example, the two compared groups are a group made of 80 patients taking an active drug (Active) and a group of 66 patients taking a placebo drug (Placebo). Once the sampling has been implemented, the total number of observations is (80 + 66) * 10000 = 1460000 observations. The corresponding dataset storing these observations has a weight of 70 Mbytes (with 5 variables). Although this may appear as a manageable dataset, keep in mind that the WPS features 8 questions, that there were 7 time points and 3 different comparisons (different active doses vs. placebo, although not presented in this paper). This amounts to a total of 70*8*7*3=11760 Mbytes, representing about 12 Gigabytes of information. Even though the COMPRESS option can be used to reduce the size of these datasets, the size remains significant, the I/O time spent to read and write these datasets will increase, and the total number of datasets will remain the same, accumulating in the study folder structure.

A possible way to address this issue is to save only one selected intermediary sampling dataset in the temporary area. By default, the re-sampling dataset corresponding to an arbitrary question, time point, and comparison (e.g., first question, first time point, and first comparison) is saved in the temporary area. These parameters can be coded as macro variables and changed later when needed. In addition, a logical switch is inserted in the program, allowing activating and deactivating the saving of this intermediary dataset. If a difference between development and validation is found, then the programmers can start by checking whether they ran their bootstrap statistics using the same sampling dataset. Once it is established that the re-sampling dataset is identical, the saving of this intermediary dataset can be deactivated. If another difference occurs and it is suspected that the sampling is causing it, the saving of the intermediary dataset can easily be implemented again for a different question, time point, and comparison. When the quality control is final, the intermediary dataset can be deleted.

2-STATISTICS MODULE

After the creation of the re-sampling, the next step consists of computing statistics for each of the *B* re-samples. This step is the most straightforward in the bootstrap process. In this example, the *t* for independent measurements is computed for each of the bootstrap replications (10000 times), as well as for the observed sample (1 time). The set of *t* coming from the replications offers an estimate of the distribution of the statistical estimator *t* under the null hypothesis. Formula 1 describes how the bootstrap *t* (called t^*) is computed where $\hat{\theta}$ is the observed mean difference while $\hat{\theta}_b^*$ is the bootstrap mean difference for Replication *b*. Formula 2 specifies the bootstrap standard error. Note that the computations for $\hat{\theta}$ and $\hat{\theta}_b^*$ can be achieved using PROC TTEST and selecting the output corresponding to the Satterthwaite method. Also note that unfortunately, this procedure does not output the corresponding bootstrap standard error $\widehat{\mathrm{SE}}_b^*$, and that this quantity will be needed later in the process to compute the confidence intervals in the variance stabilized version of the bootstrap (Section 3.2).

$$(1)\ t_b^* = \frac{\widehat{\theta}_b^* - \widehat{\theta}}{\widehat{\mathrm{SE}}_b^*} \qquad (2)\ \widehat{\mathrm{SE}}_b^* = \sqrt{(\mathrm{SD}_{yb}^{*2}/m + \mathrm{SD}_{zb}^{*2}/n)}$$

From the double-programming perspective, the programmers on both sides must ensure that they minimize the possibilities of rounding errors. Although the floating point representation of number used by most computer systems today is very powerful, it cannot represent exactly certain quantities. As a consequence of this feature, rounding errors may occur at all levels of computations. These errors are often very small but can be amplified in a succession of arithmetic operations.

Although floating point representation errors are certainly not specific to the bootstrap technique, the sheer number of computations required by such a technique clearly exacerbates the possibility of observing such errors.

Rounding error issues may emerge if the programmers do not use the exact same SAS procedure. In such a case, it is possible to obtain slightly different results from the same statistics. This type of error is even more likely when the statistics are computed using formulas rather than ready-made SAS procedures. In this case, the programmers need to agree about the order in which the computations described by the formula are performed in order to avoid different floating point errors on both sides. Cascading rounding errors have the potential to make the final conciliation of the bootstrap results challenging. For instance, the author reports a difference occurring at the third decimal point of a p-value. This level of precision is the one reported by most tables for such a variable.

To illustrate the importance of the order in which computations are performed, here are two examples in which a same percentage can be computed. The only difference is the order of execution of the operations.

$$(3)\ \frac{a}{b} \times 100 \quad \text{vs.} \quad (4)\ \frac{a \times 100}{b}$$

In Formula 3, the rounding error produced by the computation a/b is multiplied by a factor of 100. Formula 4 computes the same quantity but does not amplify the rounding error. Multiplication and division are obvious culprits, but it is sometimes difficult to ensure that rounding error is kept as small as possible. It is good to keep in mind that combining other SAS functions (for instance ABS, ROUND, LOG) may also cause rounding errors. Montgomery (2008) provides the reader with a helpful introduction on floating point representation errors as well as examples.

3-BOOSTRAP STATISTICS MODULE

The set of t_b^*, represents an approximation of the estimated distribution of the t-statistics for the mean difference of interest under the null hypothesis. Figure 2 presents an example of such a distribution. Using this distribution, it is possible to approximate the confidence interval around the observed mean difference $\widehat{\theta}$. This section will first present how to compute the confidence interval when the bootstrap is known to not be biased (no variance stabilization is necessary) as well as issues that can affect double-programming. Then, a second section will describe additional computational steps when the bootstrap is biased (variance stabilization) and its consequences on double-programming

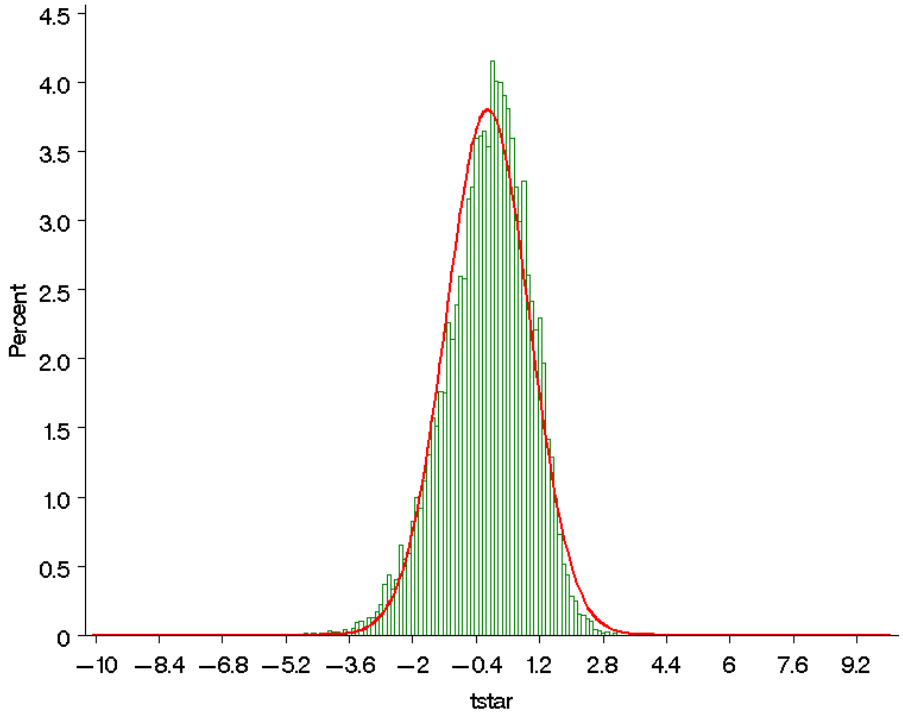


Figure 2: Example of a distribution of bootstrap t^*. In this example, 10000 replications were conducted using WPS data from one question. The Active group had 80 patients and the Placebo group had 66 patients. Note that the distribution appears symmetrical which indicates that the bootstrap should not be biased.

3.1 CONFIDENCE INTERVALS WITHOUT VARIANCE STABILIZATION

The confidence interval is computed as follows: (5) $\left(\hat{\theta} - t^*_{\left(1-\frac{\alpha}{2}\right)} S\hat{E}(\theta),\ \hat{\theta} - t^*_{(\alpha/2)} S\hat{E}(\theta)\right)$

$t^*_{\left(1-\frac{\alpha}{2}\right)}$ and $t^*_{(\alpha/2)}$ are the high and the low percentiles respectively of the t^* distribution. These percentiles are found by sorting the t^* values in an ascending order. In this example, the lowest t^* would be called t_1 and the highest t^* would be called t_{10000}. The percentiles are obtained by selecting the $\left(1-\frac{\alpha}{2}\right) \times (B+1)$ th value for the high percentile and the $(\alpha/2) \times (B+1)$ th value for the low percentile. In this example the alpha level is α=0.05 and *B* is 10000, so $t^*_{\left(1-\frac{\alpha}{2}\right)}$ is approximated by the 9750.975th value, and $t^*_{(\alpha/2)}$ is approximated by the 250.025th value. An obvious issue in this case is that the percentiles are not integer numbers. As a consequence, the low *t* percentile would be found between t_{250} and t_{251}. This implies that the programmers need to implement linear interpolation to estimate the t^* percentiles. This added step increases the program complexity and renders double-programming more difficult. To avoid this complication, choose a number of bootstrap replications that will generate integer numbers. For instance, choosing *B*=9999 instead of 10000, will change the low and the high percentiles to the 250th and 975th values of the distribution. This approach is preferred when the bootstrap program does not need to be flexible in terms of replications. If however, the number of necessary replications varies, then the added complexity of linear interpolation cannot be avoided.

When linear interpolation is required; developing a macro for such a function will greatly facilitate the double-programming. It will allow the programmers to focus on the bootstrap itself rather than on secondary aspects of the technique. The development and validation work pertaining to the macro can also be conducted in parallel by other programmers, improving overall efficiency.

3.2 CONFIDENCE INTERVALS WITH VARIANCE STABILIZATION

Previous bootstrap analyses on the WPS data (Osterhaus et al., 2009) have shown that it sometimes produced biased results. This bias occurs when the bootstrap mean difference and the bootstrap standard error are not independent. See Figure 3 for an example. As a consequence of this, the confidence interval as it is computed in the above section will be biased as well. A way to correct for the bias is to transform the data in a way that de-correlates the mean and standard error. Barber et al. (2000) describe an approximate variance stabilizing transformation method.

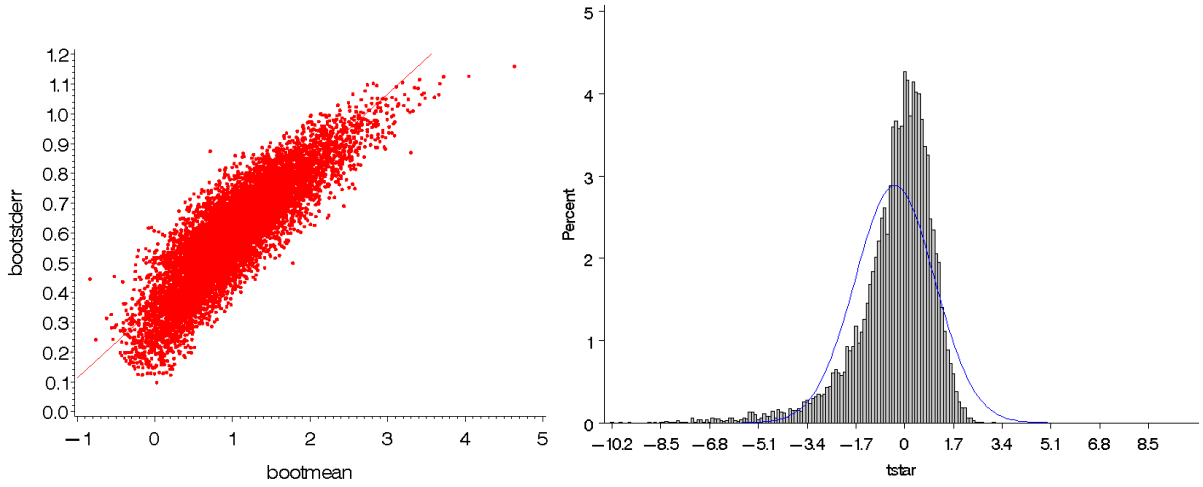


Figure 3: This figure illustrates the case where the bootstrap is biased. The left part of the figure shows the bootstrap mean difference (x-axis) as a function of the bootstrap standard error (y-axis). It shows that these two parameters are strongly correlated. The bootstrap bias caused by this correlation is clearly visible on the right part of the figure: the t^* distribution is clearly skewed to the left. Without correction (e.g., variance stabilization), the corresponding bootstrap confidence intervals will be biased.

Step 1: As a first step, estimate the relationship between the bootstrap mean difference and its standard error. Because the relationship is unlikely to be linear, it is advisable to use a non-linear technique. Perform a non-linear regression (in our example, lowess) with the bootstrap mean difference $\hat{\theta}_b^*$ as the independent variable and the standard error of the bootstrap mean difference $S\hat{E}(\theta)$ as the dependent variable. The regression function provides a smoothed approximation of the relationship between $\hat{\theta}_b^*$ and $S\hat{E}(\theta)$.
In consideration for double-programming, programmers should agree upon using the same SAS procedure so as to avoid the complexity of programming non-linear regression. PROC LOESS was used in this example.

Step 2: Then, the following variance stabilization function is applied (Tibshirani, 1988):

$$g(x) = \int^{x} \frac{1}{s(u)} \mathrm{d}u \qquad (6)$$

In this function, *s*(*u*) corresponds to the non-linear function derived in the step above and *x* corresponds to the bootstrap mean difference $\hat{\theta}_b^*$. Basically, the equation computes the area under the curve for the inverse of the lowess function. This can be done by using one of many available numeric integration techniques. In this example, the Simpson method was used, but a much simpler trapezoid method could also have been used. Although SAS provides many integration functions, they are analytical and assume that one knows the nature of the function to integrate. In this case, the integration needs to be performed numerically. As for the linear interpolation step mentioned in Section 3.1, the development and validation of an independent macro performing the integration will greatly facilitate the double-programming. As presented in our example, the integration was implemented following the Simpson method.

Step 3: Once Step 1 and Step 2 are completed, it is possible to build a look-up table matching THETAS and G(BOOTMEAN). This look-up table is used to implement the g-transformation. A consequence of the transformation is that the transformed bootstrap standard error $g(\widehat{\mathrm{SE}}_b^*)$ can be considered constant and approximately equal to 1.

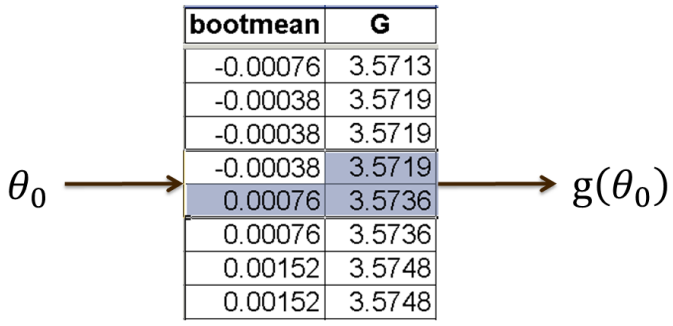
This allows for a simplification of the formulas used previously to compute the t^* and the confidence intervals. Formulas 1 and 5 can be replaced by Formulas 7 and 8 respectively:

(7) $t_b^* = \mathrm{g}(\hat{\theta}_b^*) - \mathrm{g}(\hat{\theta})$ (8) $(\hat{\theta} - t^*_{\left(1-\frac{\alpha}{2}\right)}, \hat{\theta} - t^*_{(\alpha/2)})$

The observed *t*-test (i.e., the *t* value obtained using the observed sample) will also need to be g-transformed. Although the role of the observed t-test was not previously mentioned, it is used to determine the p-value associated with the confidence interval. The derivation of the *p*-value is described in more detail in the next section (Section 3.3). Formula 9 describes the g-transformation of the observed *t*-test:

(9) $t_{obs} = \mathrm{g}(\hat{\theta}) - \mathrm{g}(\theta_0)$ with $\hat{\theta}$ being the observed mean difference and θ_0 corresponding to the value for the mean difference under the null (in this example $\mathrm{g}(\theta_0) = g(0)$).

The look-up table is used to perform the g-transformations. To operate a g-transformation, select the value x to be transformed, and select the corresponding value $g(x)$. Remember that this look-up table only contains the existing bootstrap mean difference (x). Due to this, it is not likely that the table will contain the exact values for $\hat{\theta}$ and θ_0. As a result, a linear interpolation is once again required to approximate the g-transformation. As highlited in Section 3.1, a validated macro that performs linear interpolation will be greatly beneficial to the double-programming. Figure 4 offers an example of a g-trasnformation using the look-up table.



bootmean	G
-0.00076	3.5713
-0.00038	3.5719
-0.00038	3.5719
-0.00038	3.5719
0.00076	3.5736
0.00076	3.5736
0.00152	3.5748
0.00152	3.5748

Figure 4: Description of the g-transform function using a look-up table. Note that $\mathrm{g}(\theta_0)$ is obtained via a linear interpolation because θ_0 $(with\ \theta_0 = 0)$ does not exist among the 10000 computed mean differences. The same look-up table is used for implementing the g^{-1} transformation: in this transformation, a value is read in the G column, and its corresponding value in the bootstrap mean difference column is selected.

Step 4: The t^* percentiles are found in the same way as described in Section 3.1.Once the t^* percentiles are found, the confidence intervals in the g-space can be computed. Then, the confidence intervals need to be back transformed to be used with the real observed mean. The back transformation g^{-1} is implemented with the same look-up table as before, only in the opposite direction. As for the g-transformation, linear interpolation will also be required for most data.

In summary, when the bootstrap with stabilized variance is the preferred solution, then a sizable amount of additional processing, such as linear interpolation, integration, transformation and back-transformation using a look-up table, is required. Double-programming is more efficient if these additional processes are implemented as separate macros, and not hard-coded within the bootstrap program itself.

3.3 ESTIMATING THE *P*-VALUE

Estimating the *p*-value follows the same process for both the bootstrap without variance stabilization and for the bootstrap with variance stabilization. The principle is to use the estimated distribution of the *t*-statistic under the null and compare it to the observed *t*-statistic to estimate the *p*-value associated with the observed mean difference. Formula 10 is as follows: (10) $\hat{P}_{boot} = \#\{|t_b^*| \geq |t_{obs}|\}/B$. The # symbol means "number of time such event occurs" and *B* is the number of bootstrap replications. Note that the *p*-value corresponds to a two-sided test: the absolute values of the *t*-statistics are compared.

In this last step of the bootstrap, the only factor that will affect the double-programming process is rounding error. Among the many (10000 in this example) bootstrap replications, it is likely that a given number of random samples will produce t^* very close (or even exactly equal) to the observed t_{obs}. Sometimes, the computed t^* will be only slightly different on each side, but the result of the comparison will be completely different: $t^* > t_{obs}$ and $t^* < t_{obs}$. The formula described above is a discrete transformation: although the difference between t^* and t_{obs} is very small, the difference is amplified by this transformation function. There are several options to address these discrepancies: agreeing on the order of execution of the formulas, agreeing on rounding, and finally using a criterion in the final comparison. As long as the difference between development and validation remains small enough to allow the tables or listings to remain unaffected, the outcomes can be used. However, despite making these efforts, there is always a risk that a difference will emerge for one specific set of data. In the conclusion, a way of avoiding the effect of these rounding errors is presented.

CONCLUSION

This paper described the issues and solutions encountered while validating a bootstrap-*t* analysis using double-independent programming. This paper showed the benefits of saving an intermediary dataset containing the information about the sampling, but also that it is not necessary to keep this information for all of the bootstrap comparisons. The paper also showed the benefit of keeping all aspects of the analysis as modular as possible, for the bootstrap method itself (re-sampling, bootstrap statistic distributions, *p*-value and confidence interval), or for other generic data-processing functions (linear interpolation, numeric integration, determining the percentiles, variable transformation by lookup tables). This modular approach facilitates the implementation of changes in specification: for instance a new type of sampling algorithm, or a bootstrap on different statistics (e.g. median difference instead of mean difference). The same approach can be applied advantageously to any simulation-based method calling for considerable amounts of computations.

Double-independent programming was a great tool to develop this analysis method, and allowed the programmers to become aware of errors and difficulties by implementing the same algorithm in a sometimes very different fashion. Once quality control is reached using double-independent programming, the next logical step is to transform the programs into a unique validated macro (or a set of validated macros) that can then be used by both the developer and the validator programmers. Having a validated bootstrap macro will not preclude the use of double-independent programming. Even if both sides use the same macro, there are still many opportunities to make mistakes at the level of the data input, or at the level of the macro usage.

Finally, the reader should keep in mind that the most persistent issue during the quality control was caused by floating point representation rounding errors. This paper offered some solutions for addressing these rounding errors. The most efficient method of avoiding rounding errors is the use of a unique validated macro: rounding errors are eliminated because the computations are performed in exactly the same steps on both sides.

PRO and Health Outcomes are a growing part of the work involved in clinical trials, and as the need for differentiating compounds from competitors increases, the workload increases as well. As mentioned before, these parameters often exhibit distribution answers for which standard statistical tests are not the best-suited analysis methods. As a consequence, it is likely that the use of simulation-based methods will become more frequent. Investing time in the present moment to analyze the structure of such programs promises to minimize programming time, runtime, and facilitate submission to regulation authorities.

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