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Biological variation: Evaluation of methods for constructing confidence intervals for estimates of within-person biological variation for different distributions of the within-person effect

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ABSTRACT

Background: Precise estimates of the within-person biological variation, CV_I, can be essential both for monitoring patients and for setting analytical performance specifications. The confidence interval, CI, may be used to evaluate the reliability of an estimate, as it is a good measure of the uncertainty of the estimated CV_I. The aim of the present study is to evaluate and establish methods for constructing a CI with the correct coverage probability and non-cover probability when estimating CV_I.
Method: Data based on 3 models for distributions for the within-person effect were simulated to assess the performance of 3 methods for constructing confidence intervals; the formula based method for the nested ANOVA, the percentile bootstrap and the bootstrap-t methods.
Results: The performance of the evaluated methods for constructing a CI varied, both dependent on the size of the CV_I and the type of distributions. The bootstrap-t CI have good and stable performance for the models evaluated, while the formula based are more distribution dependent. The percentile bootstrap performs poorly.
Conclusion: CI is an essential part of estimation of the within-person biological variation. Good coverage probability and non-cover probabilities for CI are achievable by using the bootstrap-t combined with CV-ANOVA. Supplemental R-code is provided online.

1. Introduction

The observed variation of the examined results from a measurand in an individual in a steady-state situation is caused by the within-person biological variation, CV_I, and the analytical imprecision, CV_A [1,2]. When using a nested ANOVA (analysis of variance) model for estimating the CV, it is assumed that the observations can be approximated by a linear combination of certain unobservable quantities known as effects [3]. Any estimate of a CV should be accompanied by a measure of uncertainty, such as the CI [4]. Good models need to be developed to be able to trust both the point estimate and its CI. As shown in a previous paper [5], a good estimate of the CV_I is possible independent of the distribution of the model effects by using the CV-ANOVA method.

When a CI is presented, it is accompanied by a confidence level, for example a 95% CI. A 95% CI implies that if the experiment were to be repeated infinite number of times the constructed CI will include the true value of the parameter in 95% of the experiments [6]. It does not imply that the specific CI covers the true value with a 95% probability, this assertion is either true or false [6]. To be able to trust the CI, the method used in constructing the CI must have been shown to have coverage probability near the stated confidence level. The CI should also have the correct non-cover probabilities for the lower and upper CI limits. An equally tailed (central) 95% CI is assumed to have non-cover probabilities of 2.5% to the left and 2.5% to the right.

The reliability of the CI depends both on the method for estimating the point estimate CV_I and the method for constructing the CI. Exact CI exists only for a few special cases, such as for the sample mean from a perfectly Gaussian distributed population with a known variance [6]. For most parameters an approximation for constructing the CI is used. When using these approximations, they might depend on assumptions regarding the distribution of the model effects. These assumptions might be difficult to fulfil even through transformation of the data, especially for data with a nested structure of the model effects as discussed in the present study.

Abbreviations: CV_I, within-person biological CV; CI, confidence interval; CV_A, analytical CV; CV_G, between-person biological CV; RCV, reference change value; ANOVA, analysis of variance; CV-ANOVA, ANOVA performed on normalized data where each person's data is divided by that person's mean value; NP, nonparametric.

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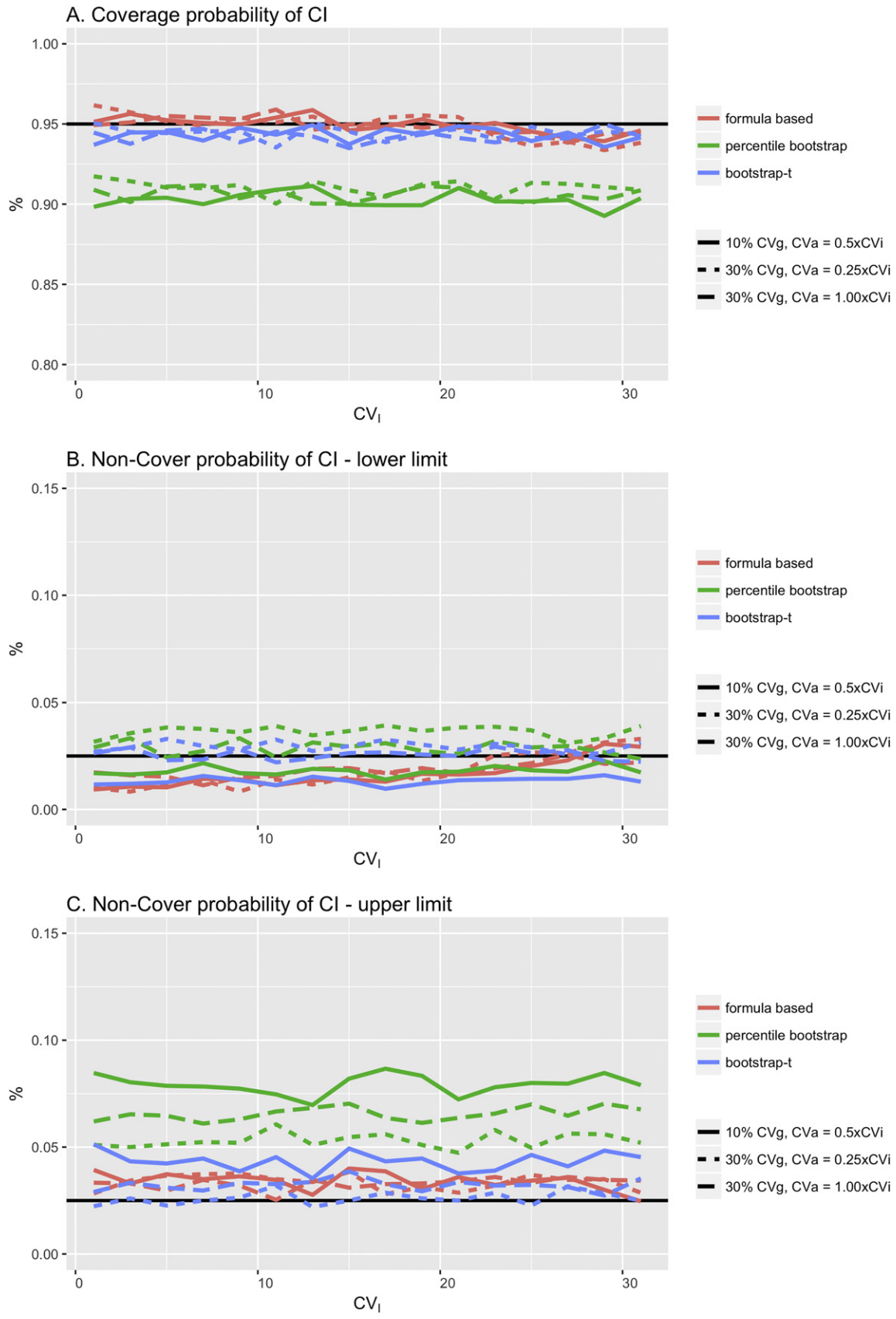

Fig. 1. Performance of CI for normally distributed within-person effects. Coverage probability (A), non-cover probabilities lower limit (B) and non-cover probability upper limit (C) with normally distributed within-person effect (Model 1) for the 3 different methods for constructing the CI (red: formula based; green: percentile bootstrap; blue: bootstrap-t) with 3 different combinations of between-subject CV (CV_G), within-subject CV (CV_I) and analytical CV (CV_A) (solid line: $CV_G = 10$ and $CV_A = 0.5CV_I$; dotted line: $CV_G = 30$ and $CV_A = 0.25CV_I$; dashed line: $CV_G = 30$ and $CV_A = CV_I$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)