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Research paper

Comparison of simulated cumulative drug versus time data sets with indices

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Abstract

The objectives of this study were twofold. First, to clarify the applicability of the similarity factor, f_2, the difference factor, f_1, and the Rescigno index, ξ_i, in the comparison of cumulative drug vs. time data sets. Second, to assess the possibility for these indices to be used on a confidence interval basis. Theoretical profiles as well as errorless and errant cumulative % data sets were simulated using the Weibull function. At various variability levels, 12-fold and 3-fold replicated reference and test data sets were generated from the errant data sets. The 90% confidence intervals were constructed for the median of the index (non-parametric confidence intervals, NPCIs) and for the evaluated index based on the 5th and 95th percentiles of 1000 index values estimated from bootstrapped samples (bootstrapped confidence intervals, BSCIs). It was observed that at low variability levels, i.e. when mean data sets can be used, all indices could be used for the comparison of cumulative data sets. At high variability levels, only the BSCIs of f_2 included the actual index value for the 12-fold replicated data sets. However, deviations of the low limits of NPCIs of f_2 from the actual index values were similar to corresponding deviations of BSCIs. When 3-fold replicated data sets were used, both NPCIs and BSCIs of all indices were generally reliable but much larger than that of 12 replications. In conclusion, the time period for the evaluation of the indices cannot be theoretically justified because indices change continuously with time. Cutoff points for their evaluation must be decided on a case-by-case basis. If theoretically possible, evaluation of the indices should be done by using areas. With highly variable data, BSCIs are preferred because compared to NPCIs they are less dependent on the number of replications. When $n = 12$, BSCIs of f_2 are comparatively more reliable. When $n = 3$, BSCIs of the indices tested in this study have similar performances.

Keywords: Cumulative profile comparison; Similarity factor; Difference factor; Rescigno index; Confidence interval

1. Introduction

Situations where a dynamic process is evaluated by actually measuring the total drug involved in the relevant process at various time points from the beginning of the process, i.e. cumulative drug vs. time data sets, are common in Pharmaceutics. Examples include the amount absorbed vs. time data sets as well as the in vitro permeability and dissolution vs. time data sets that are collected in closed systems. Although several model-dependent procedures have been proposed for the quantification of the difference between such data sets, in certain situations these may not be applicable for reasons relating to the nature or the quality of the data sets (e.g. [1,2]). In recent years the possibility of circumventing this problem with model-independent techniques has been considered using various measures of the absolute or the relative 'difference' of two profiles (e.g. [1,3]).

The similarity factor, f_2, was originally proposed for the comparison of two cumulative % dissolution profiles [4] and it has been adopted by major drug regulatory agencies worldwide [5,6]. This index is useful when the nominal plateau value of the data sets is 100; otherwise a weighting factor must be carefully introduced (e.g. [7]). A procedure has been suggested for evaluating this index on a confidence

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interval (CI) basis so that false conclusions are avoided [8]. This procedure has been applied in the comparison of actual data sets for which 12 replications per set are available and data have relatively low variability [8]. However, the ability of f_2 to reflect the true 'difference' when data sets have increased variability has yet to be investigated.

The difference factor, f_1, was proposed for testing the difference of two cumulative % dissolved vs. time profiles [4]. In contrast to f_2, evaluation of f_1 does not require the use of a weighting factor when the plateau level is different from 100 but it does require prior designation of a *reference* profile (as this will affect the relative difference of the two cumulative profiles). Also, the possibility of evaluating f_1 from data sets with increased variability has not been investigated.

The Rescigno index, ξ_i, was originally proposed for testing the difference of two plasma concentration vs. time profiles after extravascular drug administration [9,10] but it has also been considered for the comparison of cumulative drug data sets [1,11]. This index does not require the use of weighting factors (when plateau levels are different than 100) or the existence of a reference profile. The possibility of evaluating this index when data have increased variability has not been considered.

At low variability levels, i.e. when mean data can be used, all indices could be considered for the comparison of cumulative data sets. However, in the presence of highly variable data, some inference must be provided to evaluate the reliability of computed index values. If data variability is high (as a rule of thumb 15–20% coefficient of variations at early time points is usually considered borderline [5,12]) the comparison cannot be based on an index evaluated from two mean profiles because it may lead to false positive (f_2) or false negative (f_1 and ξ_i) conclusions. High data variability can be observed when the cumulative-absorbed-amount vs. time is evaluated (e.g. [13,14]), in cases where biorelevant dissolution tests are performed (e.g. [15,16]) and in permeability studies (e.g. [17,18]). The problem could be overcome with the construction of appropriate CIs.

The aim of the present investigation was twofold. First, clarify the applicability of f_2, f_1, and ξ_i in the comparison of cumulative drug vs. time data sets. Second, to test two techniques for evaluating the CIs of these indices from 12-fold and 3-fold replicated data sets with increased variability, i.e. to test the usefulness of the non-parametric CI for the median and the CI of the evaluated index using a bootstrapping technique.

2. Methods

2.1. Definition and evaluation of indices

Let $W_R(t)$ and $W_T(t)$ be the reference and test % cumulative profiles at time t, respectively. The similarity factor, f_2, is defined by the following equation [4,8]:

$$f_2(t_n) = 50\log\left[100\left(1/\sqrt{1+\frac{1}{n}\sum_{k=1}^{n} w_k[W_R(t_k)-W_T(t_k)]^2}\right)\right] \quad (1)$$

where n is the number of sampling times t_k ($k=1,2,\ldots,n$) and w_k is an optional weight factor. $f_2(t_n)$ reflects the squared distance of two data sets. The value of $f_2(t_n)$ decreases as difference between the two profiles increases.

The difference factor, f_1, is defined by the following equation [4]:

$$f_1(t_n) = \frac{\sum_{k=1}^{n} |W_R(t_k) - W_T(t_k)|}{\sum_{k=1}^{n} W_R(t_k)} \quad (2)$$

$f_1(t_n)$ reflects the sum of absolute point differences. Its value can be any positive number and it increases with the difference between the two profiles.

The Rescigno index, ξ_i, is defined by the following equation [9]:

$$\xi_i(\tau) = \left[\frac{\int_0^\tau \mid W_R(t) - W_T(t) \mid^i \cdot \mathrm{d}t}{\int_0^\tau \mid W_R(t) + W_T(t) \mid^i \cdot \mathrm{d}t}\right]^{1/i} \quad (3)$$

where i is 1 or 2, and τ is the observation interval. Depending on the value of the exponent i, $\xi_i(\tau)$ may reflect the absolute area difference ($i=1$) or the squared area difference ($i=2$) of the two profiles. $\xi_i(\tau)$ increases with the difference of two profiles and its value can be from 0 to 1.

A major difference between $f_2(t_n)$, $f_1(t_n)$ and $\xi_i(\tau)$ is that the first two take into account only the n sampling times for the profile differences, whereas $\xi_i(\tau)$ takes additionally into account the spacing between successive sampling times (by evaluating integrals over time) and, consequently, $\xi_i(\tau)$ evaluates areas. f_2 can be modified to quantify areas (for instance as proposed by Polli et al. [11]) but in this case it will not reflect the squared distance of the two data sets. However, f_1 can be modified as follows

$$f_{1,\mathrm{area}}(\tau) = \frac{\int_0^\tau |W_R(t) - W_T(t)| \cdot \mathrm{d}t}{\int_0^\tau W_R(t) \cdot \mathrm{d}t} \quad (4)$$

to quantify areas. Instead of $f_1(t_n)$, the index $f_{1,\mathrm{area}}(\tau)$ is thereby considered in this paper.

A practical decision associated with the evaluation of indices using Eqs. (1), (3) and (4) is the choice of the number of sampling times, n, or of the observation interval τ. Theoretically, one should stop sampling at a time after which the value of the index does not change. However, this never happens for f_2, because as $t_n \rightarrow \infty$ the quantity

$$\frac{1}{n}\sum_{k=1}^{n} w_k[W_R(t_k) - W_T(t_k)]^2$$

approaches 0 and, therefore, $f_2(t_n)$ approaches 100. Similarly, since the integrals $\int_0^\tau W_R(t)\cdot dt$ and $\int_0^\tau |W_R(t) + W_T(t)|^i \cdot dt$ on the cumulative profiles do not converge, $f_{1,\text{area}}(\tau)$ and $\xi_i(\tau)$ approach 0 as $\tau \rightarrow \infty$. Therefore, these indices may not be the most appropriate for the comparison of cumulative data sets because the choice for t_n or τ is possible only on a subjective basis.

2.2. The simulation model

Simulated cumulative profiles with W_0 as maximum value were obtained (SigmaPlot, 4.0 for Windows 95, SPSS Inc., IL) using the Weibull distribution function [19]:

$$W(t) = W_0 \cdot \left\{1 - \exp\left[-\left(\frac{t}{b}\right)^c\right]\right\} \quad (5)$$

with b and c the scale and shape parameters, respectively. This function has been used extensively in Pharmaceutics mainly because it allows for characterizing cumulative profiles with various shapes and it usually fits better than other functions (e.g. [19,20]).

In the current study, three shape parameters were considered, i.e., $c = 0.5$, 1 and 3. Each c was matched with three scale parameters, i.e. $b = 0.5$, 1, and 1.5. In all simulations, for a given c, two cumulative test profiles $W_T(t)$ (one with $b_T = 0.5$ and one with $b_T = 1.5$) and a reference cumulative profile $W_R(t)$ (with $b_R = 1$) were created using Eq. (5). Maximum values $W_{0R} = W_{0T} = 100$ were considered for reference and test profiles. Each test profile was compared with the reference profile using $f_2(t_n)$, $f_{1,\text{area}}(\tau)$, $\xi_1(\tau)$, and $\xi_2(\tau)$. The theoretical values of all indices were obtained with Matlab (Version 5.3, Release 11, The MathWorks Inc., MA) using the trapezoidal rule associated with a dense sampling scheme up to the time corresponding to 85% of the plateau level of the reference profile (according to previous practical recommendations [8]).

2.3. Simulated data

2.3.1. Sampling times

For a given c, the extent of observation interval was set so that at least 90% of the profile was generated in all cases. Therefore, total observation interval was 8, 4 and 2 h for c equal to 0.5, 1 and 3, respectively. In each observation interval, nine sampling points were considered. Fig. 1 shows the specific sample points and the reference and test data sets (9 in total) generated using Eq. (5).

2.3.2. Measurement error and replication of data sets

Since in most actual situations the standard deviation of error is independent of the measurement levels, the data sets shown in Fig. 1 were disturbed by an additive homoscedastic measurement error in order to obtain errant data. The added error had zero mean and standard deviation (SD) of 2, 4 and 8. Negative data were set to zero. In practice, research and quality control procedures in Pharmaceutics involve 3–12 replications per experiment. Therefore, for every data set shown in Fig. 1 and for every SD level, 12-fold replicated data sets were generated.

2.3.3. Comparison of test and reference data sets

A set of 12-fold replicated test profiles were compared with a set of 12-fold replicated reference data sets using Eqs. (1), (3) and (4). Identical comparisons were additionally performed using the first 3 replications of the test and reference set. No weighting factor was used for the evaluation of f_2. Involved integrals in $f_{1,\text{area}}(\tau)$, $\xi_1(\tau)$, and $\xi_2(\tau)$ were evaluated with the trapezoidal rule. Evaluation of indices was done up to the first sampling time after 85% of the plateau level of the reference set.

2.4. Confidence intervals

Confidence intervals of the indices were constructed with two different techniques.

The first involved the construction of a sample of index values by using all possible combinations between a test and a reference set of data. Therefore, 144-tailed and 9-tailed samples were obtained for the 12-fold and the 3-fold replicated scheme, respectively. From these samples, the median values of the index (MeNP) were computed and their 90% non-parametric confidence intervals (NPCIs) were constructed (e.g. [21]). All computations were performed with Matlab (Version 5.3, Release 11). NPCIs were determined with Minitab (Release 10Xtra, Minitab Inc., PA).

The second technique involved the application of a bootstrapping procedure. Each bootstrap sample was made from 12 randomly selected data sets from the 12-fold replicated test data sets and 12 randomly selected data sets from the 12-fold replicated reference data sets. For the selected data sets, the median test and the median reference sets were obtained. These profiles were used to evaluate one index value. 1000-tailed bootstrap samples were generated and, therefore, 1000 index values were computed. From these samples the 50th percentile (median value, MeBS), the 5th and the 95th percentiles were computed. The 90% confidence intervals for MeBS were constructed from the 5th and the 95th percentiles (bootstrapped confidence intervals, BSCIs). The same procedure was used for the first three replications of the reference and the test sets. BSCIs were constructed with Matlab (Version 5.3). This bootstrapping technique is similar to a previously used for the assessment of the confidence intervals for the similarity factor using 12-fold replicated data sets [8]. However, in this previous study [8] mean profiles and mean index values from the bootstrap samples (instead of medians) had been used.

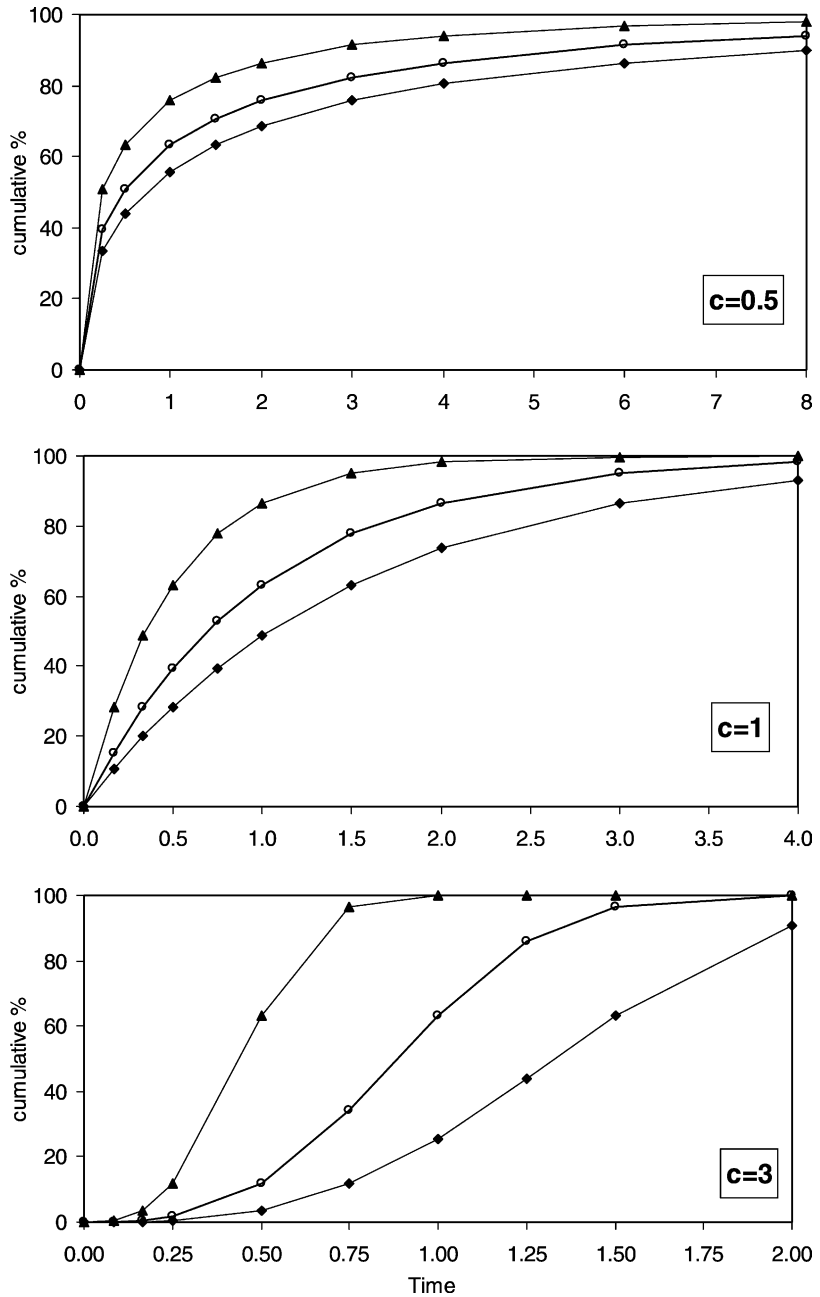

Fig. 1. The simulated errorless test data sets (◆, $b_T = 0.5$ and ▲, $b_T = 1.5$) and reference data sets (○, $b_R = 1$) used in the present study. Data sets were generated using Eq. (5).

3. Results and discussion

3.1. Applicability of indices to cumulative data sets

Since all indices change continuously with time an objective cutoff point for their evaluation is impossible. Nevertheless, when a reference set exists, indices could be meaningfully evaluated up to the time that this profile is almost complete, e.g. in practice, up to the first point after 85% completion of the reference set [8]. If the data do not allow for this cutoff rule to be applied, an alternative subjective but reasonable cutoff point must be found.

Dynamic phenomena, i.e. phenomena that occur as a function of time, should be compared using areas. Areas can be replaced by data-points only if sampling is uniform. Constant and relatively dense sampling may sometimes be feasible (e.g. when the in vitro dissolution of extended release products is studied) but in most other cases it is either not practical or not common.

The need of using areas has been pointed out previously by Rescigno [9] and Langenbucher [22] and, indirectly, by other scientists who proposed modified similarity and difference factors [11,23]. Also, the need for constant sampling time intervals has been indirectly addressed in

various guidelines for estimating the similarity factor (e.g. [5, 12]). The importance of unequal sampling time intervals when evaluating f_2 versus the buffering effect of 'areas' of the other indices can be appreciated by the discrepancy between the indices evaluated for the errorless data sets of Fig. 1 and their corresponding theoretical values. As expected, $f_{1,area}$, ξ_1, and ξ_2 evaluated from the data sets of Fig. 1 were slightly lower than their corresponding theoretical values (data not shown). Specifically, the % bias for $f_{1,area}$, ξ_1, and ξ_2 was -5.8 to -1.7%, -5.6 to -2.4% and -4.2 to -2.0%, respectively. In contrast, f_2 values of the errorless data sets were lower or higher than their corresponding theoretical values and the % bias became substantial (-18.4%) in a specific case, i.e. when $c = 3$ and $b_T = 0.5$ (Fig. 1).

3.2. Confidence intervals of the indices

Despite examples of recent publications (e.g. [24]), parametric confidence intervals for the values of f_2, $f_{1,area}$ and ξ_i are not appropriate because the sampling distributions of these indices are not known. Herein we tested the performance of these indices on the basis of CIs constructed using two different distribution-free approaches.

Fig. 2 shows the index values corresponding to the errorless data sets of Fig. 1, the median values (MeNPs) with their 90% confidence intervals, and the 50th (MeBS), 5th, and 95th percentiles of each of the 1000-tailed bootstrap samples of the indices constructed from 12-fold replicated data sets with SD = 4. Fig. 3 shows the same type of information collected using 3-fold replicated data sets. Based on Figs. 2 and 3, MeNP and MeBS values of $f_{1,area}$ ξ_1, and ξ_2 tend to be lower than the index values corresponding to the errorless data sets, i.e. MeNP and MeBS tend to underestimate the actual difference of the two profiles. The same behavior is observed at higher and lower SD levels, i.e. when SD = 8 and when SD = 2 (data not shown). With f_2 no trend could be detected.

NPCIs of the medians were narrower than BSCIs of the evaluated indices (especially when $n = 12$). Further, 3-fold replicated data sets lead to larger CIs than those constructed using 12-fold replicated data sets (especially

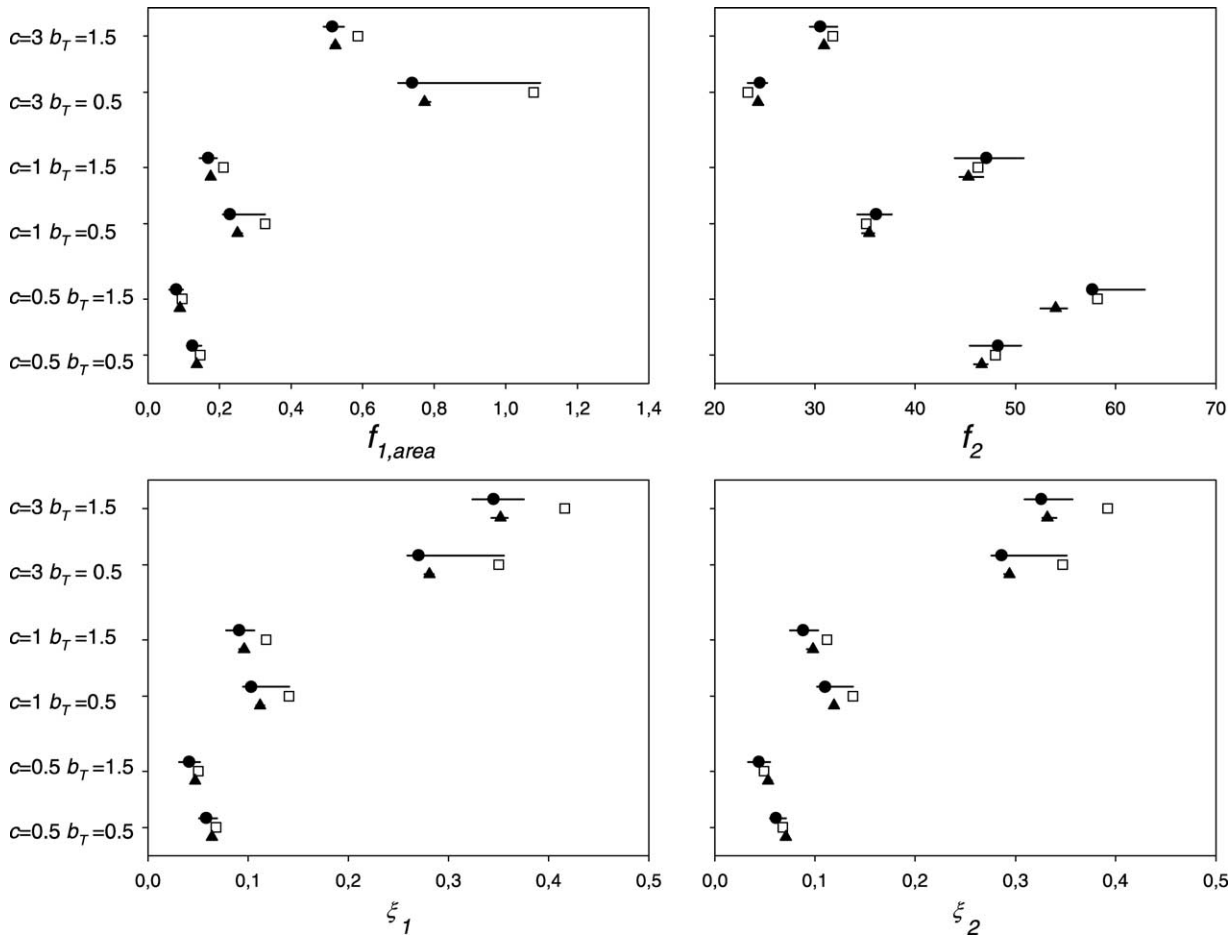

Fig. 2. The performance of f_2, $f_{1,area}$, ξ_1, and ξ_2, evaluated using 12-fold replicated data sets with SD = 4 and two different distribution-free approaches for the construction of confidence intervals. (▲) indicates the 90% non-parametric confidence interval with its corresponding median value. (●–) indicates the 5th, 50th, and 95th percentiles of a 1000-sized bootstrap sample. The square indicates the index value from the corresponding errorless data sets (Fig. 1). In all cases c is common for each pair of test and reference data sets and $b_R = 1$.

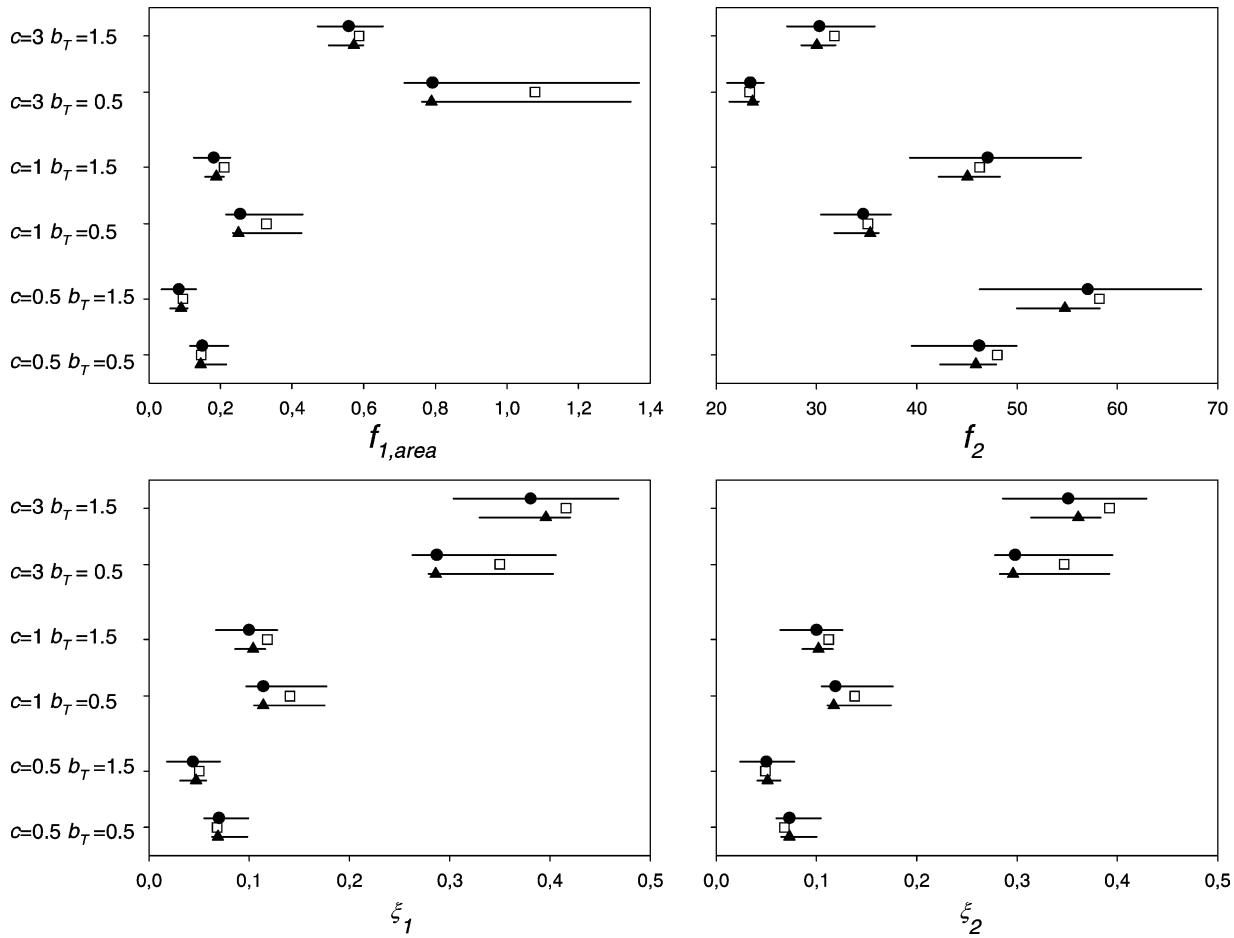

Fig. 3. The performance of f_2, $f_{1,area}$, ξ_1, and ξ_2, evaluated using 3-fold replicated data sets with SD = 4 and two different distribution-free approaches for the construction of confidence intervals. (▲) indicates the 90% non-parametric confidence interval with its corresponding median value. (●–) indicates the 5th, 50th, and 95th percentiles of a 1000-sized bootstrap sample. The square indicates the index value from the corresponding errorless data sets (Fig. 1). In all cases c is common for each pair of test and reference data sets and $b_R = 1$.

with the NPCIs). It is worth mentioning that assessment of the range and/or the degree of narrowing of the CIs with increasing the number of replications per data set on a common (for all indices) basis is impossible because the indices reflect different types of 'differences'. Only the relationship between ξ_1 and $f_{1,area}$ can be defined as shown in Fig. 4. Based on this figure a specific value of $f_{1,area}$ corresponds to various ξ_1 values. For example, $f_{1,area} = 0.20$ means that $0.091 \leq \xi_1 \leq 0.111$. The exact value of ξ_1 depends on the kinetics of the two profiles. For a given value of $f_{1,area}$ the lower limit of ξ_1 value corresponds to the case where the two profiles do not cross each other and the test is higher than the reference profile whereas the upper limit corresponds to the case where two profiles do not cross each other but the test is lower than the reference profile.

Although boundness of the true index value by the CIs should be the general requirement for a successfully constructed CI, the deviation of the lower limit of the CI of f_2 [8] and of the upper limits of the intervals of $f_{1,area}$, ξ_1 and ξ_2 from the true index value could also be used as measures of the performance of the CIs. Therefore, based on Figs. 2 and 3 (that refer to data with SD = 4) and also on similar figures (not shown) that refer to data with SD = 8 and SD = 2, the performance of CIs can be discussed as follows:

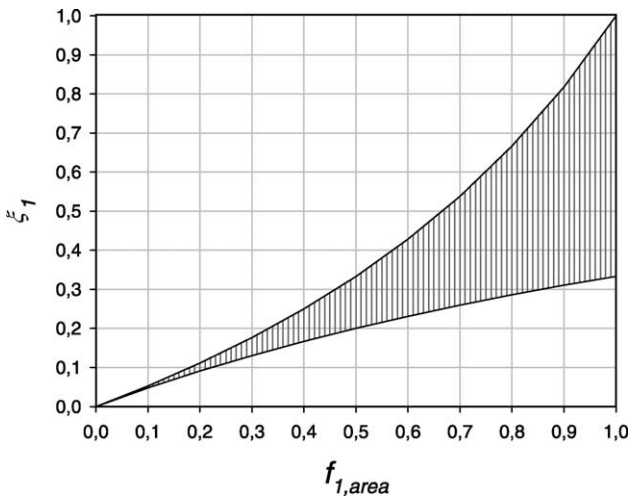

Fig. 4. Graphical presentation of the relationship between ξ_1 and $f_{1,area}$. The curves were constructed by combining Eqs. (3) and (4) and setting $i = 1$.

3.2.1. Twelve-fold replicated data sets

From a total of 72 NPCIs, the actual value, i.e. the value of the index corresponding to the errorless data sets, was included in only six cases; five cases for f_2 and one case for ξ_2. The general failure of the NPCIs to include the actual value is mainly due to their extremely narrow ranges. BSCIs included the actual index value of f_2 in all 18 cases. For $f_{1,area}$, ξ_1, and ξ_2 BSCIs included the actual index value in 9 (out of 18), 11 (out of 18) and 13 (out of 18) cases, respectively. The worst performances correspond to high SD. Further, for f_2 the deviations of the low limits of the NPCIs from the evaluated index of the errorless data were in the majority of cases similar to the deviations of the low limits of the BSCIs. In contrast, for each of the other three indices, i.e. $f_{1,area}$, ξ_1, and ξ_2, deviations of the upper limits of the NPCIs from the evaluated index of the errorless data were larger than from the corresponding deviations of the upper limits of the BSCIs.

3.2.2. Three-fold replicated data sets

From a total of 72 NPCIs, the actual value was included in 49 cases. Specifically, from a total of 18 NPCIs for each index, the actual value was included in 12 cases for f_2, 12 cases for $f_{1,area}$, 12 cases for ξ_1, and 13 cases for ξ_2. Keeping in mind that with the 12-fold replicated profiles the actual value was included in only six cases, it can be concluded that the NPCIs are strongly dependent on the number of replications per data set. With the BSCIs, from a total of 72 CIs the actual value was included in 64 cases (16 cases out of a total of 18 for each index). Further, deviations of the low limits of the NPCIs of f_2 and deviations of the upper limits of NPCIs of $f_{1,area}$, ξ_1, and ξ_2, from the evaluated indices of the errorless data were similar or lower to the corresponding deviations of the BSCIs (e.g. Figs. 2 and 3).

4. Commentary

The values of the indices studied in the present investigation change continuously with time. An objective cutoff time-point for their evaluation cannot be defined and, therefore, none of these indices is appropriate for general use in the comparison of cumulative data sets. Until alternative indices are proposed the similarity factor, the difference factor and the Rescigno index could be used as follows:

4.1. Data with low variability

In this case the comparison could be based on the mean data sets [5,12]. When a reference profile can be designated, f_2 can be used to assess the squared distance of the two data sets. However, a weighting factor must be carefully introduced if the plateau level of the reference profile is not 100 [7]. Between $f_{1,area}$ and ξ_i the former is preferred because, in contrast to ξ_i, it reflects directly the specific relative difference of the test from the reference profile. When a reference data set does not exist $f_{1,area}$ is inappropriate and only f_2 and ξ_i can be considered. However, the inability to define an objective cutoff limit requires their evaluation to be done on a subjective, reasonable, case-by-case basis. For example, in biorelevant in vitro tests a physiologically relevant time period seems reasonable, whereas in quality control dissolution testing the completion time of the fastest profile can be considered [5,6]. Another issue that requires some attention is that the evaluation of f_2 involves the evaluation of differences of data points (not areas); therefore, *time* is not taken into account unless relatively dense, equally spaced, sampling time intervals are utilized.

4.2. Data with high variability

In this case the index should be evaluated on a CI basis. BSCIs are preferred because, compared to NPCIs are less dependent on the number of replications. In the 12-fold replicated scheme, f_2 evaluated on the basis of the BSCI appears to be the most reliable index for the comparison of cumulative data sets. However, apart from issues relevant to the applicability of this index (described above for the low variability scenario), one should also keep in mind that, if the nominal plateau value of the data is not known (e.g. [25]), this index is inappropriate. In the 3-fold replicated scheme, all indices could be evaluated on the basis of their BSCIs. Selection of the most appropriate should be based on the recommendations described above for the 'low-variability' scenario.

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