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TALKING POINTS

IVIVC: Indices for Comparing Release and Response Profiles

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An important aspect of in vivo–in vitro correlation (IVIVC) is to quantify the difference between two time profiles, typically from a reference formulation R and a test formulation T. The problem exists likewise for release curves in vitro and plasma profiles in vivo. The goal is a single-value index that summarizes the differences between the two profiles, where $n = 1$ to N paired data points. R_n and T_n are usually observed at identical time points t_n.

- In 1992, Rescigno (1) proposed the following index for the bioequivalence of two plasma time profiles:

$$\xi_i = \left[\int_0^\infty |R(t) - T(t)|^i dt \Big/ \int_0^\infty |R(t) - T(t)|^i dt \right]^{1/i}$$

  An alternative definition ξ^* replaces the integrals by a numerical summation over the observed differences.
- In 1996, Moore and Flanner (2) proposed two indices for comparing dissolution profiles:

$$f_1 = \left(\frac{\sum |R_n - T_n|}{\sum R_n} \right) \times 100\%$$

$$f_2 = 50 \log\{[1 + 1/N \sum (R_n - T_n)^2]^{-0.5} \times 100\}$$

  These represent an averaged difference, obtained by summing over all data points, $n = 1$ to N.

In the subsequent literature (3–5), features of these indices have been discussed. However, there are still some open questions that need clarification.

1. Although ξ_i was originally proposed for *differential* plasma profiles, and f_1 and f_2 for *cumulative* release profiles, this distinction must not be regarded as a general restriction. In fact, all indices can be used likewise for release and response distribution functions, in differential as well as cumulative form (see Fig. 1). (Note that release profiles are sometimes given as probability density function (pdf), and response may be reported as cumulative distribution function (cdf) (e.g., cumulative urinary excretion).
2. Mathematical practice would suggest a definition of indices f_1 and f_2 in terms of *fractions* rather than *percentages*. This way, the formulas are easier to read and free from the confusing factor ‘‘100.’’ Note that percentages are not more than a display format of fractions, used for input or output (e.g., 10% for 0.1 or 100% for 1).
3. When averaging a set of differences (deviations), we have the choice to average absolute values (ME, mean error) or squared values (RMSE, root mean squared error; SD, standard deviation). The index f_1 reflects a mean error as the sum of absolute deviations. In contrast, f_2, re-

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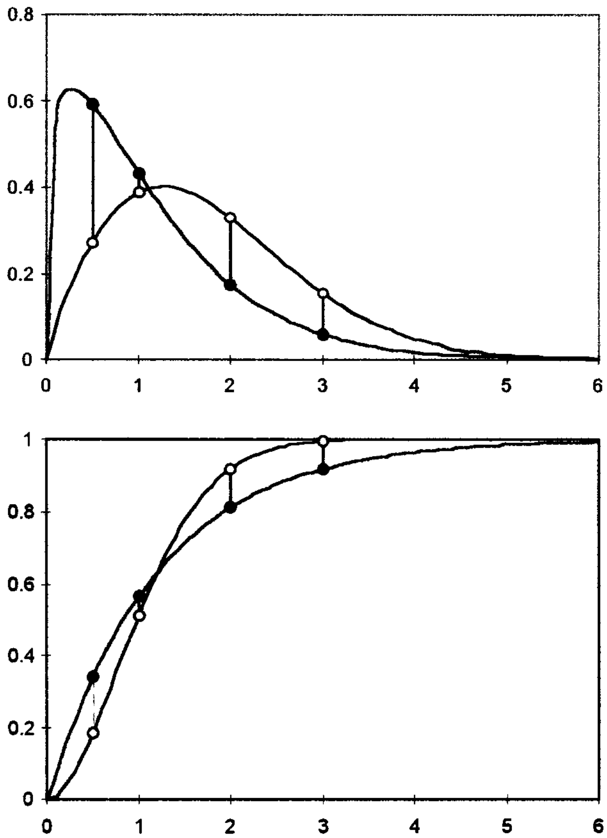

Figure 1. Computation of differences between two distribution curves. Top: probability density functions (pdf); bottom: cumulative distribution functions (cdf).

flects a root mean square error (i.e., the root of the sum of squared deviations). The Rescigno index ξ_i covers both cases (as well as others), by proper choice of the exponent: $i = 1$ gives the absolute error, $i = 2$ the squared error.

4. It is common statistical practice to quantify *differences* rather than *similarities*. That is, standard deviation or coefficient of variation provides a scale for which ''0'' represents identity, increasing positive values indicate increasing dissimilarity. If ordinate values are scaled properly, the scale has an upper end of ''1'' for complete dissimilarity. Indices ξ_i and f_1 conform with this general practice.

However, f_2 differs in that it provides a similarity scale (4,5) for which identity is expressed as ''100,'' complete dissimilarity as approximately ''0.'' In addition, a borderline value of 10% between ''similar'' and ''dissimilar'' (which seems reasonable for release data) is transformed to approximately ''50'':

RMSE	f_2	f_2'
0.00	**1.0000**	1.0000
0.01	0.9247	0.7500
0.02	0.8253	0.6920
0.05	0.6463	0.5942
0.10	**0.4989**	0.5000
0.20	0.3492	0.3840
0.50	0.1505	0.1883
0.70	0.0774	0.1018
0.90	0.0229	0.0312
1.00	**−0.00001**	0.0000

The general usefulness of such a transformation is questionable: It is felt that it is less transparent and more confusing than the original difference scale. If it were felt useful, it should be applied also to f_1 and other indices to make them commensurable. In this case, the clumsy f_2 transformation should be replaced by

$$f_2' = 1 - f_1^{\log 2} = 1 - f_1^{0.30103}$$

which is easier to apply and produces exact values for all three pivotal points.

5. When comparing time profiles, it is important to include the time dimension, that is, the time and the duration over which differences are found. Integral forms such as curve moments (e.g., mean time) or ξ_i take this into account by assessing areas between the curves. Indices such as f_1 and f_2 simply average differences, disregarding the time scale. Thus, an important feature of the data is lost in the analysis. As a consequence, improper choice of data points may lead to misleading conclusions.

6. The published indices illustrate various ways to average sums of deviations and to relate them to the means themselves:

- f_2 divides by N and is thus on the level of a mean deviation, similar to a standard deviation. In contrast, f_1 and ξ_i divide by a sum of values, that is, express the mean difference as *relative* to the mean (similar to a coefficient of variation).
- f_1 is obtained from a division by $\sum R$, that is, the mean of the reference profile. This definition is asymmetric in that one of the profiles is identified as reference R. Different indices are found depending on whether $T < R$ or $T > R$.
- The Rescigno index ξ uses a division by $\sum(R + T)$, that is, the mean of both profiles. This definition is symmetric in that both profiles are treated as equivalent. It gives the same index for both cases.

The proposed indices represent a small selection from a manifold of possibilities combining the power applied for summation, the relation to the number of observations, and the scale chosen for representation.

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