

# Qualitative Analysis Using Near-Infrared Spectroscopy

## A Comparison of Discriminant Methods in Dissolution Testing

The bootstrap error-adjusted single-sample technique (**BEST**) is shown to perform better than the Mahalanobis distance metric in qualitative **near-IR** analysis. The BEST algorithm is designed for high-speed parallel processing supercomputers, but is also shown to operate efficiently on single processors. Using hypothetical **multivariate** data, the bias and RSD of the BEST and Mahalanobis metrics were compared as a function of the number of dimensions in hyperspace and the number of training samples in the calibration set. Full **near-IR** spectra of intact pharmaceutical tablets were analyzed successfully using the BEST to predict the tablet **dissolution** rate. The BEST metric is calculated more rapidly and more precisely than the Mahalanobis metric when full **near-IR** spectra are employed in qualitative analysis.

**N**ear-infrared (near-IR) spectroscopy has been used in quantitative and qualitative applications in chemical and pharmaceutical research. Recently, there has been great interest in the chemical and pharmaceutical industries in instituting near-IR methods as quality-control tests because of the technique's speed and nondestructive nature.

Qualitative applications of near-IR spectroscopy depend on pattern recognition to analyze the multivariate data that are generated by the spectrometer. Qualitative near-IR methods using Mahalanobis distances (1,2), soft independent modeling of class analogies (SIMCA) (3,4), and the bootstrap error-adjusted single-sample technique (BEST) (5-7) have all been discussed in the near-IR literature. Pharmaceutical applications of qualitative **near-IR** spectroscopy include identity and quality testing of raw materials (8), detection of tablet and capsule tampering (9,10), detection of tablet degradation (7), analysis of **parenteral** products (11), and others (12).

Principal-component analysis (PCA) or other methods that incorporate data reduction (such as partial least-squares) must normally be used to transform the spectral matrix into a manageable size. The transformation procedure usually concentrates information about the analytes onto 10 or fewer factors (dimensions) with the largest **eigenvalues**, while the remainder of the factors are eliminated (in the hope that the remaining factors contain mostly noise). The ability of the BEST to analyze full spectra containing hundreds of wavelengths eliminates the need for this data-reduction step and simplifies qualitative analysis by near-IR spectroscopy.

This study compares the bootstrap error-adjusted single-sample technique and Mahalanobis distance metrics in qualitative analysis of near-IR data. The BEST is shown to offer improved speed, accuracy, and **precision** over the Mahalanobis distance algorithm (which is commercially available, commonly used, and has been accepted by the Food and

Drug Administration [FDA] in a new drug application [NDA] for analyzing a veterinary lincomycin product [13]). Tests of both metrics (employing orthogonal synthetic and actual pharmaceutical data) in the following study demonstrate qualitative analysis using both techniques.

### QUALITATIVE NEAR-IR METHODS

The BEST metric is employed as an asymmetric, anisotropic unit vector in wavelength space or in principal-axis space. The BEST is an improved version of the BEAST (5), a cluster-analysis technique for exploring multivariate distributions of spectra in **hyperspace**. The BEST avoids the difficulty of setting a hypercylinder radius empirically by incorporating equations that determine the hypercylinder radius from each new set of bootstrap replicates. The BEST distance between the centroid of a calibration (training set) spectral cluster and a sample spectrum is proportional to the concentration(s) of the sample constituent(s) that generate the vector connecting the centroidal and **sample** spectral points. The direction of the vector provides the spectrum that identifies the constituent(s) of the sample. The BEST is **nonparametric** and makes no assumptions about the distribution of spectral points in hyperspace.

In near-IR spectral data analysis, all implementations of the BEST begin with the collection of a "training set" of samples. The training set consists of spectral data values (log  $1/R$ , absorbance, and so forth) recorded at  $d$  wavelengths for  $n$  training samples. The resulting data are represented by a two-dimensional (2-D)  $n \times d$  matrix.

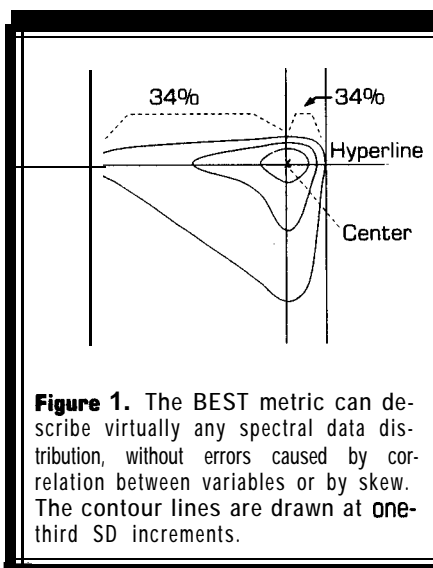
The BEST comprises two operations:

- The bootstrap distribution is calculated from the  $d$ -dimensional training-set spectra using as many computational processors as are available. This bootstrap distribution forms the basis for calculating directional probabilities, and is calculated only once for each calibration set. The bootstrap distribution for the calibration set and the **centroid** (group mean) of the bootstrap **distrib-**

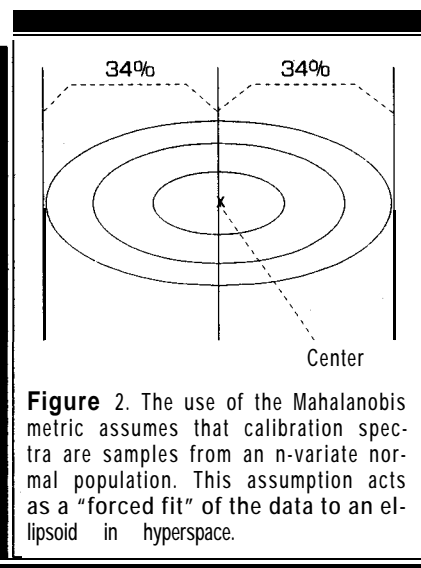


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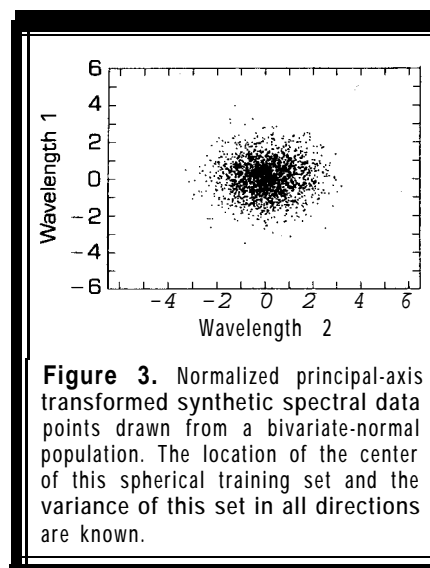
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**Figure 1.** The BEST metric can describe virtually any spectral data distribution, without errors caused by correlation between variables or by skew. The contour lines are drawn at one-third SD increments.



**Figure 2.** The use of the Mahalanobis metric assumes that calibration spectra are samples from an n-variate normal population. This assumption acts as a "forced fit" of the data to an ellipsoid in hyperspace.



**Figure 3.** Normalized principal-axis transformed synthetic spectral data points drawn from a bivariate-normal population. The location of the center of this spherical training set and the variance of this set in all directions are known.

but both are used in the routine analysis of samples with the BEST.

- The BEST distance, in units of multidimensional standard deviations (SDs), is calculated using the calibration set, the bootstrap distribution and center (from the preceding operation), and the spectrum of the test sample. The Euclidean distance from the center (C) of the bootstrap distribution to the test spectrum (X) is scaled by an element of the probability vector  $\sigma_c$  in the direction of X to give the distance to the test spectrum in BEST SDs.

$$SDs = \left( \sum_{j=1}^d (c_j - x_j)^2 \right)^{1/2} / \left( (\sigma_c^x / |z_\alpha|) n^{1/2} \right) \quad [1]$$

The number of calibration samples is given as  $n$ , and the selected contour (confidence) level is given in  $|z_\alpha|$  (5). Figure 1 depicts the asymmetric "stretch" of the BEST "rubber yardstick" and represents the variety of problematic distributions that the BEST can accurately describe.

Discriminant analysis in qualitative near-IR spectroscopy can also be accomplished using the Mahalanobis metric (1,2). The Mahalanobis distance value is also based on the entire set of training-sample spectra. Given a test-sample spectrum, a Mahalanobis distance value with units of multidimensional SDs is calculated by

$$[(X - C)^T (\text{cov} T)^{-1} (X - C)]^{1/2} = d_m \quad [2]$$

Figure 2 depicts the elliptical spectral distributions that the Mahalanobis metric is meant to describe. The Mahalanobis "rubber yardstick" has a symmetric "stretch" around the centroid of spectra in hyperspace, limiting its utility for complex samples with variable constituents.

Both the BEST and the Mahalanobis distances are used to determine whether two spectral groups (for example, samples or constituents of samples) appear near one another in spectral hyperspace. When the distance between groups of spectra of similar size is determined, the distance must be greater than six SDs to verify the hypothesis that the clusters are different.

The Mahalanobis distance metric assumes that the spectral variations associated with both the calibration set and the test spectra are random. However, spectral noise is often random, particularly in the analysis of complex mixture samples. In order for the Mahalanobis distance to function correctly, the spectral clusters must all share the same shape in spectral hyperspace. Furthermore, these clusters must *not* be skewed. As a consequence, near-IR spectral discrimination using Mahalanobis distances is likely to fail when the sample is a complex mixture with many variables involved in the sampling procedure (such as sample temperature, changing constituent concentrations, variable optical alignment, and scattering from particles of different sizes in the sample matrix). For these reasons, the BEST metric is employed in difficult near-IR imaging problems such as the fiber-optic analysis of atheromas in living arterial tissue (14).

## EXPERIMENTAL

**Instrumentation.** The near-IR spectrophotometer used was an InfraAlyzer 500 (Bran + Luebbe, Elmsford, NY) with modifications from Applied Acoustics (Wilmington, DE). The monochromator scanned the 1100–2500-nm spectral range. Data analysis was performed with an IBM 3090-600J parallel vector supercomputer. The IBM 3090 used software written in Speakeasy IV Zeta (Speak-

easy Computing Corporation, Chicago, IL).

The reference values for the tablet dissolution rate were determined using a VanderKamp 600 six-spindle dissolution tester (Van-Kel Industries, Edison, NJ) after the near-IR spectrum of each tablet was obtained. The Type II apparatus was used in accordance with the United States Pharmacopeia (USP) dissolution guidelines for carbamazepine. The dissolution medium consisted of 900 mL of distilled water containing 1% sodium lauryl sulfate and no more than 1% methanol. The solutions were maintained at 37 °C. The paddles were allowed to rotate at 75 rpm.

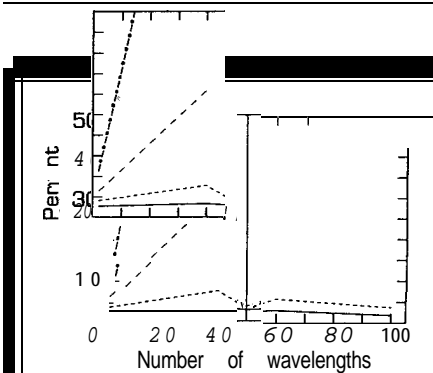
A "hydrator" — a desiccator in which the desiccant was replaced with water — was used to control the atmospheric conditions surrounding the tablets. The tablets were exposed to moisture by placing them in uncapped scintillation vials and supporting the vials over distilled water inside the closed glass hydrator.

**Materials.** The carbamazepine tablets used (Tegretol, lot number 1T130122) were purchased from Ciba-Geigy (Summit, NJ).

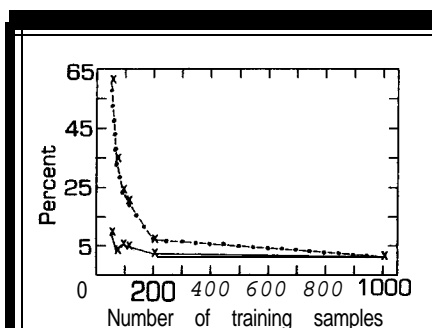
## RESULTS AND DISCUSSION

**Comparison methods.** The BEST and Mahalanobis distance algorithms were compared for accuracy and precision as a function of the number of wavelengths observed in the spectra and the number of samples employed in the training set. The American Society for Testing and Materials (ASTM) E456 definitions of accuracy and precision were employed (15). Both synthetic spectral data and actual pharmaceutical spectral data were examined.

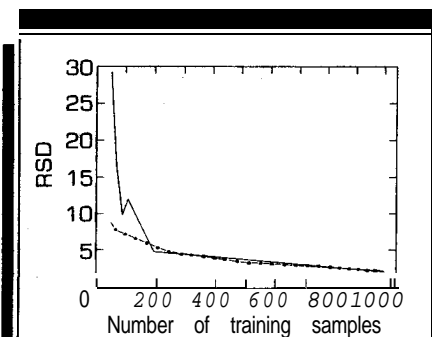
The synthetic spectral data (Figure 3) were drawn randomly from an orthogonalized normal population with centroid at the origin and correlation matrix equal to I. The true location of the calibration set's mean as well as the vari-



**Figure 4.** The Mahalanobis metric fails as the number of wavelengths in the training set approaches the number of training samples. The BEST bias is shown as a short-dashed line, the BEST RSD as a solid line, the Mahalanobis bias as a dashed-dotted line, and the Mahalanobis RSD as a long-dashed line.



**Figure 5.** The effect of training-set size on the Mahalanobis and BEST metrics. The BEST bias appears as a solid line and the Mahalanobis bias as a dashed-dotted line.



**Figure 6.** The effect of training-set size on the Mahalanobis and BEST metrics. The BEST RSD (%) appears as a dashed-dotted line and the Mahalanobis RSD (%) as a solid line.

ance of the group in all directions was, therefore, known exactly. Wherever possible, normalized, principal-axis-transformed spectral data points were examined. In such a space, the unit vector is one SD of the calibration set. The BEST hypercylinder radius encompassed 100% of the bootstrap replicates. Because the distance between the synthetic test samples and the center of the synthetic calibration set were known exactly, the accuracy and precision of the BEST and Mahalanobis metrics were compared readily using the difference between the *computed* distance of the test spectrum from the centroid and the *true* distance.

Figure 4 compares the accuracy and precision of qualitative measurements made with the Mahalanobis and BEST metrics as a function of the number of wavelengths used in the analysis. The training set contained 50 samples (represented by the vertical line); 1000 bootstrap replications were used in the BEST. The Mahalanobis metric (the dashed-dotted line) shows large biases and RSDs even for spectra containing a small number of wavelengths. The BEST metric shows a low, and essentially constant, bias and RSD over the range of wavelengths used. As the number of wavelengths of observation approaches the number of samples in the training set, the performance of the Mahalanobis metric declines rapidly. When the number of wavelengths exceeds the number of training samples, the Mahalanobis calculations cannot be performed because the required matrix inversion (see equation 2) cannot be completed. When the number of wavelengths exceeds the number of samples, transformation of the spectra to principal axes can be employed to reduce the dimension of spectral hyperspace, enabling calculation of Mahalanobis distances. Unfortunately, in reducing dimension, some wavelengths are always weighted down to zero in the transformation matrix, destroying new peaks with critical information. The importance of avoiding the assignment of zero weight to some wavelengths is demonstrated in the prediction of the dissolution rate of tablets (which we discuss later).

In Figure 5, the accuracy of the Mahalanobis and BEST metrics are compared as a function of the training-set size using a constant number of components or orthogonal wavelength dimensions (30 dimensions in the case shown) and 1000 bootstrap replications. The BEST metric performs better than the Mahalanobis metric over the entire range — from 50 to 1,000 training samples.

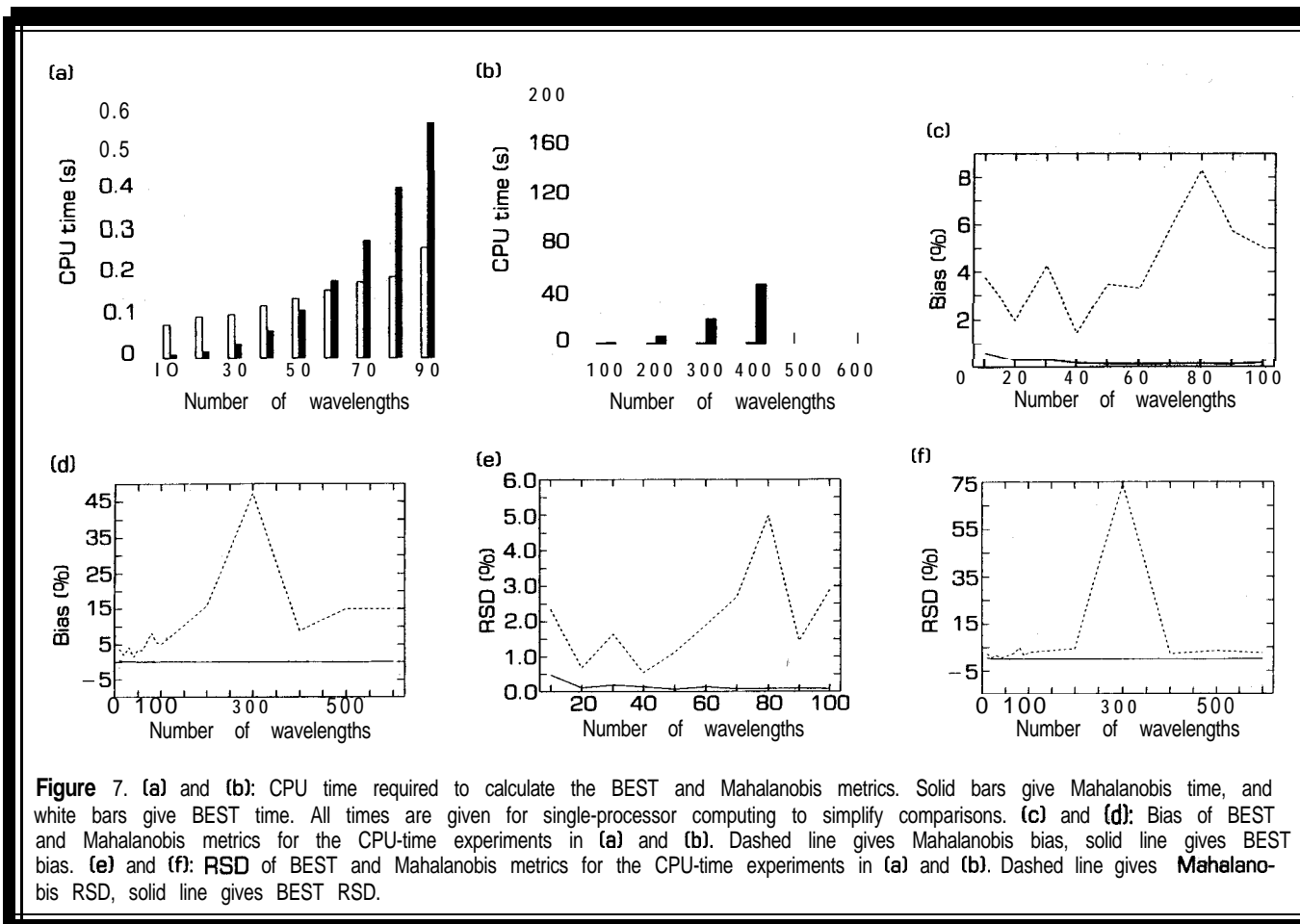
Figure 6 displays the RSD of the Mahalanobis and BEST metrics as a function of the number of samples in the training set. Once again, 30 orthogonal dimensions and 1000 bootstrap replications were used to analyze

each training set. For training sets with fewer than 200 samples (and most applications involve training sets with fewer than 200 samples) the BEST metric shows better RSD values. The BEST and Mahalanobis metrics display similar RSD values for training sets that contain more than 200 samples.

The bar graphs in Figure 7 demonstrate that the BEST metric is not only more accurate and precise than the Mahalanobis metric, but it is often calculated more rapidly as well. The matrix inversion required by the Mahalanobis metric is usually accomplished by algorithms whose complexity (in terms of number of operations required) increases as the number of principal components or wavelengths cubed. In contrast, the complexity of the BEST metric increases linearly with the number of principal components or wavelengths. While the "overhead" in setting up the BEST calculation is greater than for the Mahalanobis, by the time the spectral data are of 60 or more dimensions, the BEST metric is calculated more rapidly. Full near-IR spectra with continuous coverage from 1100 to 2500 nm use at least 141 wavelengths on a typical commercial spectrometer. In each test case used in Figure 7, the training set was *n*-variate normal and the test spectrum was exactly 100 SDs from the center of the training set. The number of samples in the training set always exceeded the number of components or dimensions by three. In each case, the number of BEST bootstrap replications was 1000. The Mahalanobis metric shows its instability through varying bias and RSD values. The BEST metric has a uniformly lower bias and RSD than the Mahalanobis metric. The time required to calculate principal-component scores was not included in the figures. The superior bias and RSD of the BEST becomes even more notable in full-spectral analysis involving hundreds of wavelengths.

**Full-spectra accuracy and precision.** Figure 8 describes the bias and RSD of the BEST metric alone as a function of the number of training samples used in the qualitative analysis. Ten orthogonal wavelength dimensions or principal components were employed in each training set. The RSD is low over the range of training set sizes from 10 to 10,000. The bias is lower with the larger training sets and is always reasonable ( $\pm 5\%$  or less) with training sets containing  $>25$  samples in spite of the low number of bootstrap replications (1000) employed to generate Figure 8.

The bias and RSD of the BEST metric as a function of the number of bootstrap replications are illustrated in Figure 9. The number of bootstrap replications varied from 1000 to 100,000. Each calibration set contained 100 sample spectral points examined in 141 orthogonal dimensions. The RSD and bias



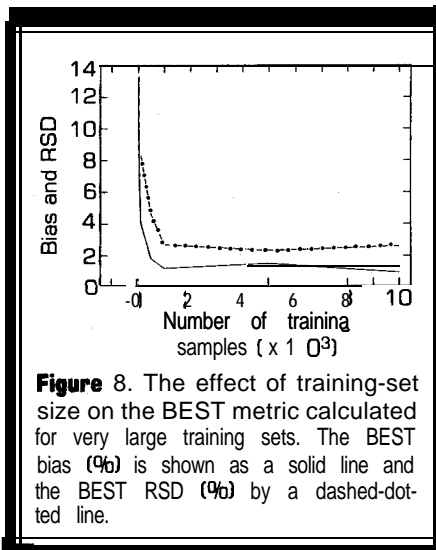
**Figure 7.** (a) and (b): CPU time required to calculate the BEST and Mahalanobis metrics. Solid bars give Mahalanobis time, and white bars give BEST time. All times are given for single-processor computing to simplify comparisons. (c) and (d): Bias of BEST and Mahalanobis metrics for the CPU-time experiments in (a) and (b). Dashed line gives Mahalanobis bias, solid line gives BEST bias. (e) and (f): RSD of BEST and Mahalanobis metrics for the CPU-time experiments in (a) and (b). Dashed line gives Mahalanobis RSD, solid line gives BEST RSD.

were fairly constant over the entire range. The replication process is the most central processing unit (CPU)-intensive portion of the BEST calculations. Therefore, it is wise to use the minimum number of replications required to obtain the necessary accuracy. Generally, large numbers of replications are needed only

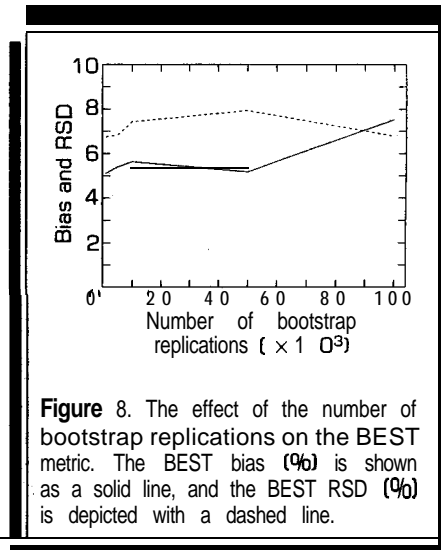
when training sets are skewed in a hyperspace of hundreds of dimensions. The use of 1000 replications usually gives good precision without sacrificing excessive amounts of CPU time in the calculations.

The variation of the bias and RSD of the BEST metric with the number of wavelengths

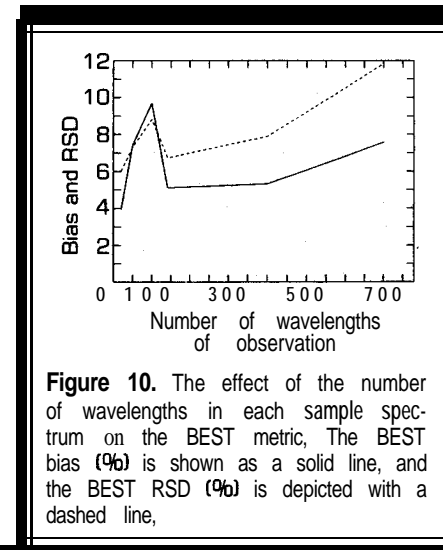
of observation or dimensions in hyperspace is shown in Figure 10. Each training set contains 100 samples from which 1000 bootstrap replications are calculated. The RSD and bias increase slightly as more dimensions are included in the calibration set. As the volume of the analytical hyperspace increases (as it



**Figure 8.** The effect of training-set size on the BEST metric calculated for very large training sets. The BEST bias (%) is shown as a solid line and the BEST RSD (%) by a dashed-dot line.

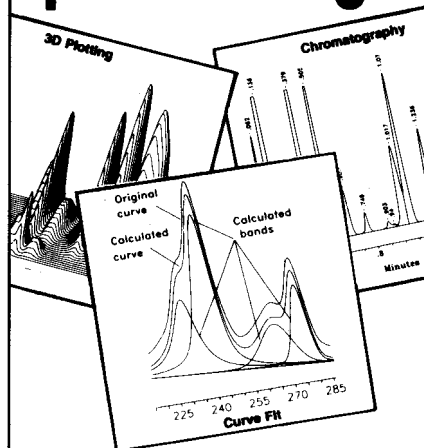


**Figure 8.** The effect of the number of bootstrap replications on the BEST metric. The BEST bias (%) is shown as a solid line, and the BEST RSD (%) is depicted with a dashed line.



**Figure 10.** The effect of the number of wavelengths in each sample spectrum on the BEST metric. The BEST bias (%) is shown as a solid line, and the BEST RSD (%) is depicted with a dashed line.

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does with more wavelengths), progressively more bootstrap replicates are required to adequately describe that hyperspace. Using a constant number of replications (as in this plot), the bias and RSD increase slowly as the number of spatial dimensions increases.

**Qualitative analysis of full spectra with the BEST.** Figure 11 describes the use of BEST and Mahalanobis algorithms with actual pharmaceutical samples. Full near-IR spectra (701 wavelengths) were used in Figure 11 to classify single, intact carbamazepine tablets (a drug used in the treatment of seizures) according to their dissolution rate. The full near-IR spectrum (1100-2500 nm in 2-nm increments) of each training and test tablet was recorded prior to the destruction of the tablet in a USP-standard dissolution test. The tablet spectra were obtained using a unique reflector that simultaneously illuminated all of the surfaces of the tablet. The training set comprised nine carbamazepine tablets with a slow dissolution rate ( $\sim 15 \mu\text{g mL}^{-1} \text{h}^{-1}$  in a USP-standard test). The test tablets had dissolution rates ranging from  $\sim 165 \mu\text{g mL}^{-1} \text{h}^{-1}$  (tablet 1) to  $17 \mu\text{g mL}^{-1} \text{h}^{-1}$  (tablet 12). The actual dissolution rates of tablets 1-12 (to the left of the horizontal dashed line) decreased steadily. Tablets 13-21 had a dissolution rate similar to that of the training set.

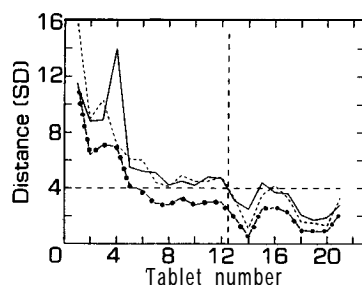
The curves display a similar trend for the three distance metrics. The horizontal long-dashed line represents a 98% confidence limit

on the training set, and demonstrates that full near-IR spectra can be used for qualitative analysis with the BEST even when the number of training samples is very much smaller than the number of wavelengths. The BEST metric correctly identifies tablets 1-12 (100% accuracy) as having a different dissolution rate than the training tablets (whether full spectra or data from two principal components are employed). However, the Mahalanobis metric identifies 7 of 12 (58%) of the tablets with a different dissolution rate incorrectly. Tablets 15 and 16, which were flagged by the BEST as having higher dissolution rates, actually turned out to have slightly higher dissolution rates than the mean rate of the training set ( $\#15 = 14.4 \mu\text{g mL}^{-1} \text{h}^{-1}$ ,  $\#16 = 17.4 \mu\text{g mL}^{-1} \text{h}^{-1}$ , while the mean for the training set was  $13.6 \mu\text{g mL}^{-1} \text{h}^{-1}$ ). However, this difference in rate was not statistically significant, and the spectra of these tablets showed a baseline deviation that was significantly different from that of the training set. The BEST metric detected this baseline deviation, which probably arose from the positioning of the tablet in the reflector.

Analysis of full spectra eliminates the need for a data reduction step (for example, principal-axis transformation) in the calculation. In fact, the full spectral analysis increases the sensitivity of the BEST, because the wavelengths that are often considered to contain little analyte information and that are normally discarded (that is, given little weight) through principal-component analysis (or other methods) are not eliminated. In many cases, the use of a small number of principal components to model a phenomenon results in a loss of critical information. The dissolution rate of carbamazepine during the first four days of exposure to moisture (the period in which dissolution rate changes most dramatically) can be modeled well with the factors that correlate to moisture (16). After four days, however, a new peak in the aldehyde region of the spectrum appears in the tablet excipients (16). This new information is given zero weight in the principal component model, resulting in a loss of ability to predict the dissolution rate and in the loss of important information about the fundamental processes involved in the degradation of the tablets. The BEST algorithm does not miss the new peak information because all of the wavelengths are weighted equally all of the time.

## CONCLUSIONS

The large-scale performance of the BEST and Mahalanobis metrics as a function of training-set size and the number of wavelengths of observation has been determined using a parallel supercomputer. The BEST performs better than the Mahalanobis algorithm in terms of



**Figure 11.** BEST and Mahalanobis distances separating tablets with a different dissolution rate. The solid line represents the BEST distance calculated in a 701-D space, the short-dashed line represents BEST distances calculated in a 2-PC space, and the dashed-dotted line represents Mahalanobis distances calculated in the same 2-PC space. The horizontal long-dashed line represents a 98% confidence limit on the distances. The tablets to the right of the vertical long-dashed line have the same actual dissolution rate as the training tablets, and the tablets to the left do not.

speed, accuracy, and precision. The number of replications is a primary factor in determining the precision of the BEST method. The number of samples used in the training set is the major factor affecting the accuracy of the BEST method. Full near-IR spectra containing hundreds of wavelengths are analyzed easily using the BEST, thereby eliminating the data-reduction step that is normally employed in near-IR methods.

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ing exploratory mathematical studies aimed at solving the "false-sample" problem in thought-like operations on parallel processors. These studies have led to a new near-IR imaging technology that is now being applied to in vivo studies of the role of apolipoproteins in atherogenesis.

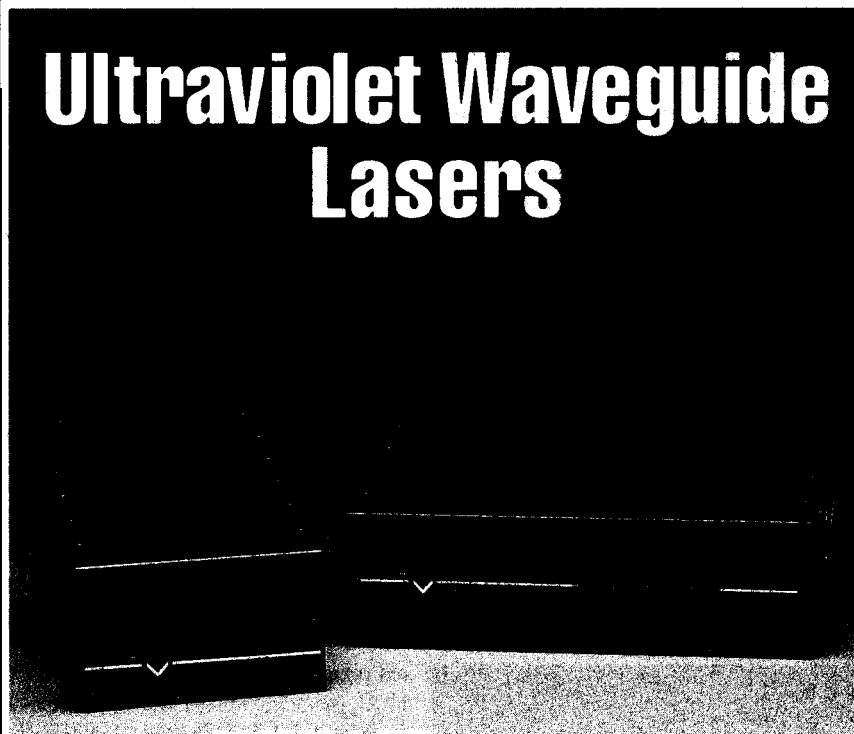
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