An Information-Based Computational Technique for Estimation of Chromatographic Peak Purity

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Received November 19, 2006

Assessment of the purity of chromatographic peaks is an important step in developing and validating purification procedures for complex mixtures. While curve-fitting techniques can be useful for determining the retention times and relative concentrations of the components of a chromatographic peak, their utility is limited by the lack of unambiguous criteria for determining the number of such components. In this work, we present a computational technique for analyzing chromatograms to estimate the number of components, their retention times, and their relative concentrations. In contrast to Fourier-transform-based techniques, the technique we present does not require manual peak identification. It is based on curve-fitting and uses the Akaike information criterion to estimate the number of components. Application of the technique to chromatograms obtained from size-exclusion and reverse-phase chromatography of test mixtures indicates that it is useful for the characterization of complex mixtures.

INTRODUCTION

In some chromatographic applications, the presence of coeluants is common and possibly even unavoidable. In applications such as proteomics, metabolomics, and environmental analysis, the nature of the samples dictates that hundreds or thousands of distinct analytes will be present. These coeluants cause overlapping peaks, thus generating the need for methods to assess the purity of chromatographic peaks. Various computational techniques currently exist to assist in the interpretation and analysis of chromatograms of complex mixtures.[1−6] Recent developments in this area include the use of genetic algorithms,[7] neural networks,[8] and the generalized rank annihilation method.[7]

The basic problem solved by the computational techniques is deconvolution. Deconvolution aims to reverse the distortion caused by the chromatographic apparatus, which conforms approximately to a spreading—a convolution—of the input followed by additive measurement noise. Deconvolution problems arise routinely in many branches of science and engineering (e.g., astronomy, seismology, and communications), and a multitude of deconvolution techniques exists. As such, one of the key issues in any deconvolution problem is determining which technique is appropriate for the problem at hand.

The assessment of chromatographic peak purity is no exception: any computational technique for the assessment of chromatography peak purity that is to be routinely useful must account for the specifics of its deconvolution problem. Many of the standard deconvolution techniques (such as the fast Fourier transform) fail in this regard because they are designed to deconvolve signals formed from the convolution of two more or less general time signals, while the input signal that gives rise to a chromatogram is not a general time signal: it is a point process—a signal that consists only of impulses. In the input signal of a chromatogram, these impulses correspond to the various components of the mixture. A deconvolution technique that assumes that the input signal is a general time signal rather than a point process does not immediately output the true quantities of interest: the retention times and relative concentrations of the various components. Thus, a manual inspection of the deconvolution result is necessary, which is not only tedious but also a potential source of error.

One method that does account for the input signal being a point process is regression, or curve fitting, which attempts to find the best fit for the sum of a number of peaks to the chromatogram. Regression is a useful approach that does, indeed, immediately yield an estimate of the retention times and relative concentrations of the various components. When the number of components is known, the use of artificial neural networks (with connections optimized by an evolutionary algorithm) allows very precise and accurate estimation of relative concentrations even when the component peaks are highly overlapping.[8] However, when the number of components is not known, curve fitting requires a robust parsimony criterion to determine the number of peaks to fit to the chromatogram, and such criteria are often not present. Thus, curve-fitting approaches can fail to fulfill what is often the most important task in the assessment of chromatographic peak purity: robustly determining the number of components.

Existing techniques for deconvolution of chromatograms have addressed the problem of estimating the number of

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10.1021/ci6005195 CCC: $37.00
Published on Web 07/12/2007

components in a variety of ways. Constrained iterative relaxation,[2] a method based on Fourier deconvolution of the chromatogram, requires estimation of the number of components (e.g., by curve fitting or manual inspection) after deconvolution. Deconvolution of chromatograms using a maximum entropy criterion[5] allows the number of components to vary on the basis of an additional χ-squared criterion: increasing the precision of the fit requires a larger number of components. However, the coefficient that determines the relative influence of these two criteria must be chosen by the investigator on the basis of prior knowledge of what a physically reasonable number of components would be.

One effective way to estimate the number of components in a sample is to make use of a second data variable, such as an absorption spectrum, associated with the chromatographic retention time. Analytical techniques such as eigenvalue plots,[6] the orthogonal projection approach,[1] and classical and genetic algorithm-based optimization[7] have been used to determine the numbers of components and their amounts. These approaches perform well when analytes are spectrally distinct, since the information contained in the spectral variable allows poorly resolved peaks to be assigned with low uncertainty.

For analytes such as peptides and nucleic acids, however, absorption and fluorescence spectra tend to be very similar for each member of the class, making the use of a second data variable difficult without sophisticated detection techniques such as NMR or mass spectrometry. Deconvolution of univariate chromatograms in a way that robustly estimates the number of components is likely to be useful for such analytes. Deconvolution techniques that account for the input signal being a point process have been described.[9−11] These methods are, however, not specifically designed for the assessment of chromatographic peak purity, and it is not apparent that they would perform well for this purpose.

In this paper, we propose a new computational technique for the assessment of chromatographic peak purity. Our technique estimates the number of components in a chromatogram as well as the retention times and relative concentrations of these components. We estimate the number of components by using a standard statistical criterion for selecting among competing models, the Akaike information criterion (AIC).[12] Using the AIC effectively depends critically on a proper choice of the competing models, and this modeling choice is an integral part of our technique. We applied our technique to several chromatograms of known, artificial mixtures and found that the technique performs favorably on a wide variety of mixture compositions.

MATERIALS AND METHODS

C18 Reverse-Phase Chromatography. A total of 10 peptides were chromatographed individually using a C18 column (Phenomenex Jupiter column, 150 × 4.6 mm). The column was equilibrated in buffer A (3% acetonitrile, 0.1% trifluoroacetic acid), and the peptides were eluted using a gradient of 9.7% buffer B/min (where buffer B is 100% acetonitrile, 0.1% trifluoroacetic acid). The chromatograms of these 10 peptides were normalized and averaged to obtain a basic peak function. The retention time and full width at half-height for each peptide were determined using the average of three trials. Three peptides were then chosen [angiotensin II antipeptide, thrombin receptor activator for peptide 6 (TRAP-6), and ACTH fragment 4-11] to form eight different test mixtures in which the three peptides were present in a variety of ratios (see Table 1). To allow the analysis to be carried out without prior knowledge of extinction coefficients, relative concentrations are expressed in absorbance units. These test mixtures were chromatographed in triplicate.

Table 1. Measured Retention Times (RT) and Relative Concentrations (rel. conc.) of the Three Components of the C18 Chromatography Test Mixtures, and Retention Times/Concentrations as Estimated by the AIC[a]

mixture #	RT (min)	est. RT (min)	rel. conc.	est. rel. conc.
		Mixture 1		
component 1	20.88	20.94 ± 0.01	0.25	0.25 ± 0.04
component 2	21.19	21.26 ± 0.01	0.46	0.51 ± 0.06
component 3	21.28	21.37 ± 0.02	0.29	0.24 ± 0.05
		Mixture 2		
component 1	20.88	20.93 ± 0.01	0.91	0.92 ± 0.10
component 2	21.19	21.30 ± 0.07	0.06	0.08 ± 0.05
component 3	21.28		0.04	
		Mixture 3		
component 1	20.88	20.95 ± 0.02	0.25	0.28 ± 0.04
component 2	21.19	21.34 ± 0.01	0.07	0.72 ± 0.08
component 3	21.28		0.68	
		Mixture 4		
component 1	20.88	20.92 ± 0.02	0.25	0.26 ± 0.04
component 2	21.19	21.23 ± 0.01	0.68	0.68 ± 0.07
component 3	21.28	21.42 ± 0.07	0.07	0.06 ± 0.04
		Mixture 5		
component 1	20.88	20.92 ± 0.01	0.25	0.28 ± 0.04
component 2	21.19	21.22 ± 0.02	0.19	0.18 ± 0.05
component 3	21.28	21.32 ± 0.01	0.56	0.54 ± 0.06
		Mixture 6		
component 1	20.88	20.89 ± 0.01	0.25	0.27 ± 0.04
component 2	21.19	21.20 ± 0.01	0.56	0.56 ± 0.06
component 3	21.28	21.32 ± 0.03	0.19	0.17 ± 0.04
		Mixture 7		
component 1	20.88	20.90 ± 0.02	0.25	0.28 ± 0.04
component 2	21.19	21.20 ± 0.03	0.13	0.12 ± 0.06
component 3	21.28	21.30 ± 0.01	0.63	0.60 ± 0.07
		Mixture 8		
component 1	20.88	20.86 ± 0.01	0.25	0.25 ± 0.04
component 2	21.19	21.17 ± 0.01	0.63	0.64 ± 0.07
component 3	21.28	21.31 ± 0.04	0.13	0.10 ± 0.04

[a] The relative concentration of the peptides is calculated after normalizing their quantities to adjust for differences in extinction coefficient. The intervals given are 95% confidence intervals.

Computation. Our computational technique was implemented using Matlab version 7.1. The Matlab scripts that form the program are available at http://web.mit.edu/dslun/www/chrom_rest.zip. The program was run on computers with Intel Pentium-class processors operating on the Microsoft Windows XP operating system.

THEORY

The basic model of a chromatogram is that $f(t)$, the chromatogram produced by the mixture of n components, is given by

$$f(t) = \sum_{k=1}^{n} a_k g_k(t) + \epsilon_0(t) \qquad (1)$$

where a_k is the concentration of component k, $g_k(t)$ is the chromatogram produced by pure component k, and ϵ_0 is a noise term that represents the measurement error in $f(t)$.

In curve-fitting approaches, it is typically assumed that $g_k(t)$ is known, say, $g_k(t) = g(t - t_k)$, where $g(t)$ is the basic peak caused by a single, pure component ($g(t)$ is frequently referred to as the impulse response or the point-spread function). Given n, curve fitting yields estimates of a_1, ..., a_n and t_1, ..., t_n.

But $g(t)$ is not known precisely. Like the chromatogram $f(t)$ itself, $g(t)$ *must* be obtained by measurement. Moreover, the hypothesis that $g_k(t) = g(t - t_k)$, for all components k, is often violated because of variation in the basic peak shape. In our technique, we instead assume that

$$g_k(t) = g(t - t_k) + \epsilon_k(t) \tag{2}$$

where $\epsilon_k(t)$ represents both measurement error and possible deviation about the basic peak for component k. This modification in assumptions, while seemingly minor, is an important component of our technique; by using a more accurate model of the chromatogram, we are able to perform inference more accurately.

We have

$$f(t) = \sum_{k=1}^{n} a_k[g(t - t_k) + \epsilon_k(t)] + \epsilon_0(t) = \sum_{k=1}^{n} a_k\, g(t - t_k) + \epsilon(t) \tag{3}$$

where

$$\epsilon(t) = \sum_{k=1}^{n} a_k\, \epsilon_k(t) + \epsilon_0(t) \tag{4}$$

After sampling, we obtain

$$f[m] = \sum_{k=1}^{n} a_k\, g_{t_k}[m] + \epsilon[m] \tag{5}$$

where $f[m]$, $g_{t_k}[m]$, and $\epsilon[m]$ are $f(t)$, $g(t - t_k)$, and $\epsilon(t)$, respectively, sampled at the time of sample m. Moreover, we have

$$\epsilon[m] = \sum_{k=1}^{n} a_k \epsilon_{t_k}[m] + \epsilon_0[m] \tag{6}$$

For simplicity, we suppose that ϵ_{t_k} and ϵ_0 are white Gaussian processes. While it is almost certainly true that ϵ_{t_k} and ϵ_0 do not conform to the distributions of white Gaussian processes in reality, this modeling assumption greatly enhances the tractability of the problem and, as we shall see, results in a technique with good empirical performance nonetheless. In particular, we suppose that $\epsilon_{t_k}[m]$ is an independent, zero-mean Gaussian random variable of variance ${\sigma_{t_k}}^2[m]$ and that $\epsilon_0[m]$ is an independent, zero-mean Gaussian random variable of variance ${\sigma_0}^2[m]$. Thus, it follows that $\epsilon[m]$ is a zero-mean Gaussian random variable of variance $\sum_{k=1}^{n} {a_k}^2\, {\sigma_{t_k}}^2[m] + {\sigma_0}^2[m]$.

We estimate the parameters of interest, $\{a_k\}$ and $\{t_k\}$, using a maximum likelihood (ML) estimate, which, in this case, is given by

$$\underset{\{a_k\},\{t_k\}}{\operatorname{argmin}} \sum_{m} \frac{\left(f[m] - \sum_{k=1}^{n} a_k\, g_{t_k}[m]\right)^2}{\sum_{k=1}^{n} {a_k}^2\, {\sigma_{t_k}}^2[m] + {\sigma_0}^2[m]} \tag{7}$$

for any given n. We have not included n in the estimate because the likelihood is only increased by increasing n. Thus, positive infinity is always a maximum likelihood estimate for n. This is not an acceptable estimate for n, since we expect that there must be some natural principle of parsimony at work. Therefore, we select n in a separate model selection step, using the AIC[12] to determine the most appropriate value. The AIC is a widely used statistical criterion for model selection that seeks to minimize the Kullback−Leibler (KL) distance[13] or information divergence between the true probability distribution of a system and that obtained by an estimated model. More precisely, the AIC gives an unbiased estimate of the average KL distance between the two distributions, and by finding an optimal estimate with respect to the AIC, we obtain an estimate for the true probability distribution, naturally yielding the desired parsimony criterion (since the true probability distribution does, in fact, arise from a parsimonious system).[14]

We propose the following algorithm: We take, as input, a candidate range for n, $n_{\min} \le n \le n_{\max}$. For each value of n in this candidate range, we find maximum likelihood estimators, $\{a_k^{\mathrm{ML}}\}$ and $\{t_k^{\mathrm{ML}}\}$, by solving minimization problem 7 using random-restart gradient descent.[15] Random-restart gradient descent will not necessarily find an optimal solution to problem 7, but it will find a solution that corresponds to a local minimum of the objective function and, given sufficient run time, finds an optimal solution with high probability. The number of restarts that random-restart gradient descent requires in practice depends upon both the optimization problem and the manner in which the initial conditions are chosen for each restart. If the initial conditions are chosen randomly over the feasible domain of the variables to be optimized, then the number of restarts can be determined empirically by repeatedly running the algorithm for a fixed number of restarts, then increasing this number until a consistent outcome is observed. For the problem at hand, we have found that 20 restarts generally suffice.

We score the result for n using the AIC:

$$\mathrm{AIC}_n = 4n + \sum_{m} \frac{\left(f[m] - \sum_{k=1}^{n} a_k^{\mathrm{ML}}\, g_{t_k^{\mathrm{ML}}}[m]\right)^2}{\sum_{k=1}^{n} a_k^{\mathrm{ML}}\, {\sigma_{t_k^{\mathrm{ML}}}}^2[m] + {\sigma_0}^2[m]} \tag{8}$$

The value of n that minimizes AIC_n along with its corresponding $\{a_k^{\mathrm{ML}}\}$ and $\{t_k^{\mathrm{ML}}\}$ are chosen as the solution to the problem; that is, we estimate that the chromatogram in question is produced by the mixture of n components, where component k, for $k = 1$, ..., n, has amplitude a_k^{ML} and is centered at time t_k^{ML}.

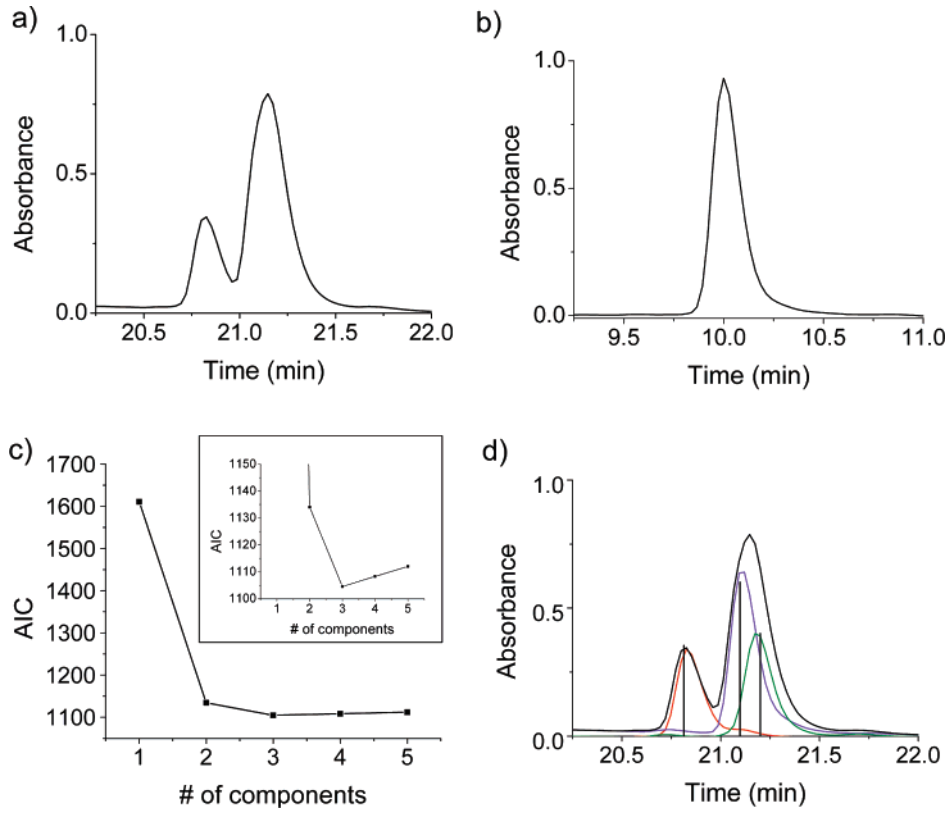

Figure 1. Deconvolution of C18 chromatogram. (a) Mixture 1 (composed of three peptides: ACTH fragment 4-11, angiotensin II antipeptide, and TRAP-6) chromatographed on a C18 column. (b) Average peak shape function found by normalizing and averaging the traces of 10 standard peptides. (c) The AIC predicts the presence of three peaks underlying the observed chromatogram of mixture 1. The local minimum (inset) is well-defined; the apparent shallowness of the region around the minimum is due to the very high AIC values for component numbers less than the number of well-resolved features (e.g., one component for mixture 1). (d) Shown is an overlay of the mixture 1 chromatogram (black line), the underlying component peaks (ACTH fragment 4-11 shown in red, angiotensin II antipeptide shown in blue, and TRAP-6 shown in green), and the positions and amplitudes of underlying peaks predicted by the AIC (black bars).

By observing the form taken by AIC_n, the importance of our assumption regarding the basic peak shape becomes apparent: If, instead of eq 2, we make the more common assumption that $g_k(t) = g(t - t_k)$, then we obtain the ML estimate

$$\underset{\{a_k\},\{t_k\}}{\operatorname{argmin}} \sum_m \frac{(f[m] - \sum_{k=1}^{n} a_k g_{t_k}[m])^2}{\sigma_0{}^2[m]} \tag{9}$$

and AIC_n is given by

$$\mathrm{AIC}_n = 4n + \sum_m \frac{(f[m] - \sum_{k=1}^{n} a_k^{\mathrm{ML}} g_{t_k^{\mathrm{ML}}}[m])^2}{\sigma_0{}^2[m]} \tag{10}$$

We see that we obtain a much simpler expression for the ML estimate, which can be solved simply by least-squares curve fitting, but the AIC tends to favor substantially more complicated (less parsimonious) models, which, on the basis of our observations, are generally false.

In the above algorithm, f, σ_0, $\{g_{t_k}\}$, and $\{\sigma_{t_k}\}$ are obtained by measurement. We take f and σ_0 to be the sample mean and sample standard deviation of several replicate measurements of the chromatogram, and we likewise obtain $\{g_{t_k}\}$ and $\{\sigma_{t_k}\}$ from several replicate measurements of the chromatograms of various standard peptides.

RESULTS AND DISCUSSION

We validated our technique using C18 reverse-phase chromatography (validation on size-exclusion chromatograms is described in the Supporting Information). Test mixtures composed of three peptides with overlapping peaks were prepared. A chromatogram of a typical test mixture can be found in Figure 1a. In addition, a list of the components along with their retention times and relative concentrations is found in Table 1. Note that the chromatogram has only two distinguishable peaks, despite the fact that it is a three-component mixture. In order to perform our deconvolution, we derived an average peak function by averaging the chromatograms of 10 standard peptides. The basic peak function is shown in Figure 1b.

The result of our deconvolution technique applied to a typical mixture (mixture 1) is shown in Figure 1. (See Table 1 for the result of the deconvolution technique applied to all eight test mixtures.) From Figure 1c, we see that the best AIC score is obtained when the number of peaks is three. In Table 1, we show the estimated retention times and relative concentrations of the three predicted peaks. In addition, these estimated parameters are compared graphically to the actual retention times and amplitudes of the underlying components in Figure 1d. The estimated retention times correspond closely to the measured retention times, and for two of the

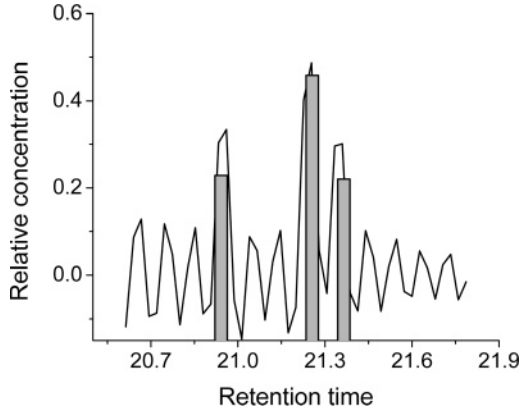

Figure 2. Comparison of Fourier transform-based (solid line) and AIC-based (gray bars) deconvolutions of test mixture 1.

three components, the estimated and measured retention times agree to within the 95% confidence intervals.

The estimated relative concentrations of all three components in mixture 1 agree to within their 95% confidence intervals with the true relative concentrations of the underlying components. We believe that the accuracy of the deconvolution, both in the estimates of retention times and in relative concentrations, is principally due to the small uncertainty in the peak width for the C18 standard peptides. The average full width at half-height of the C18 standard peptides was 0.16 ± 0.01 min (standard deviation = 6% of the average).

One of the major limiting factors in the precise estimation of component quantities is likely to be uncertainty in the peak width arising from specific interactions of individual peptides with the matrix. For size-exclusion chromatography, where experimental uncertainties in peak width are larger than in C18 reverse-phase chromatography, the precision and accuracy of estimation is lower (see the Supporting Information). The relative concentrations of components within a broad feature become difficult to estimate when the peak width is highly variable, because the estimate of the relative concentrations depends on an estimate of the components' relative contributions to the total feature width. For example, it may not be possible to determine whether a broad feature comprises two peaks of approximately equal width (corresponding to components of equal concentration) or one broad peak and one narrow peak (corresponding to components of unequal concentration).

To explore the scope of the AIC deconvolution in detecting minor components, we examined eight mixtures of varying compositions (Table 1). The deconvolution identified all three components for six of eight test mixtures; the two components it failed to identify were present at relative concentrations of <10%. However, in one test mixture, a component of relative concentration <10% was successfully detected. For components of relative concentration ranging from 10 to 60%, the relative concentration was consistently estimated correctly within the 95% confidence interval of the estimation (10−20% of the estimated value, with lower relative uncertainties for higher relative concentrations). Thus, the AIC method performs well on the test chromatograms when unresolved components are present at relative concentrations of ≥10% but can fail to detect smaller unresolved components.

To determine whether the performance of the AIC-based method was comparable to that of previously reported methods, Fourier-transform-based deconvolution of the test mixtures was also carried out. Estimation of the relative concentrations is comparably accurate for the two methods (Figure 2). The method of truncating the high-frequency components used here led to comparatively large oscillations in the estimated baseline, but more sophisticated approaches to the problem of high-frequency components have been used successfully.[2] The major disadvantage of Fourier-transform-based deconvolution methods is the necessity for manual peak identification following deconvolution, which in some cases is nontrivial and a potential source of error. In contrast, AIC-based deconvolution provides robust estimations of numbers of components and their relative concentrations without an additional peak identification step.

CONCLUSIONS

We provide here a novel deconvolution method for assessing chromatographic peak purity. This new technique estimates the number of components in a chromatogram along with the retention times and relative concentrations of these components using the AIC, a standard statistical criterion for selecting among competing models. Here, using a variety of test mixture chromatograms, we show that this technique can accurately determine the number of components in a given mixture and can reasonably predict the retention times of these underlying components. The technique can also determine the relative concentrations of the underlying components when the standards used for estimation are sufficiently homogeneous in their peak widths/shapes. Overall, this technique should prove to be useful in assessing chromatographic peak purity for many types of chromatography. This information-based technique is expected to be particularly useful for analytes such as peptides and oligonucleotides, for which the chromatographic properties of large sets of diverse standards can be characterized statistically.

ACKNOWLEDGMENT

This work was supported by the National Science Foundation under grant CCF 05-14869. Funding for work in the Licht laboratory was provided by the MIT Department of Chemistry.

Supporting Information Available: Additional details describing the application of the deconvolution method to size-exclusion chromatograms. This information is available free of charge via the Internet at http://pubs.acs.org.

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CI6005195