Multivariate Visualization of Chromatographic Systems

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ABSTRACT

Chromatography is a technique used to separate and quantify the components in a complex chemical mixture. We have created a 3D visualization system capable of comparing the chemical properties of chromatographic systems. The visualization system combines scatter plots, parallel coordinates, and specialized glyphs to assist in the analysis of chromatographic data and comparisons of multiple systems. Using this tool, numerous separation systems can be readily compared simultaneously – greatly facilitating the ability to select systems that are likely to produce desired separations during method development.

1. INTRODUCTION

Chemists are often faced with the challenge of separating and quantifying the molecules in a complex mixture. Pharmaceutical companies, for example, must test formulations for impurities and make certain the drug contains the correct amounts of active ingredients. There are hundreds of chromatographic systems to choose from when developing analytical methods. Therefore, to avoid wasting time and money, it is vital that method development be guided by chemical principles rather than by trial and error.

This manuscript is broken into four main sections. In the first, we describe chromatography and the practical problem we are trying to solve. In the second, we discuss several methods for visualizing multivariate data, including glyphs, triangle plots, and parallel coordinates. We then describe a 3D visualization tool created to analyze large sets of chromatographic data. As detailed in that section, our approach combines scatter plots, parallel coordinates, and specialized glyphs to assist in the analysis of the data. In the final section, we demonstrate the utility of the visualization tool by applying it to two chromatographic data sets.

2. BACKGROUND AND MOTIVATION

2.1 Chromatography

Chromatography is used to separate components in a mixture. In this technique, the mixture is introduced into a column filled with small particles. The different compounds in the mixture have different affinities for the particles (i.e., they participate in different types and strengths of intermolecular interactions). As solvent flows through the column, compounds with weaker affinities for the particles move down the column faster than compounds with stronger affinities. Thus, the various compounds in the mixture are separated based on their relative affinities for the solid particles. A detector (such as a spectrophotometer or mass spectrometer) positioned at the end of the column produces a signal that is proportional to the amount of each compound present (see Figure 1). Thus, compound identification and quantification are achieved from the order of elution and the magnitude of the signal.

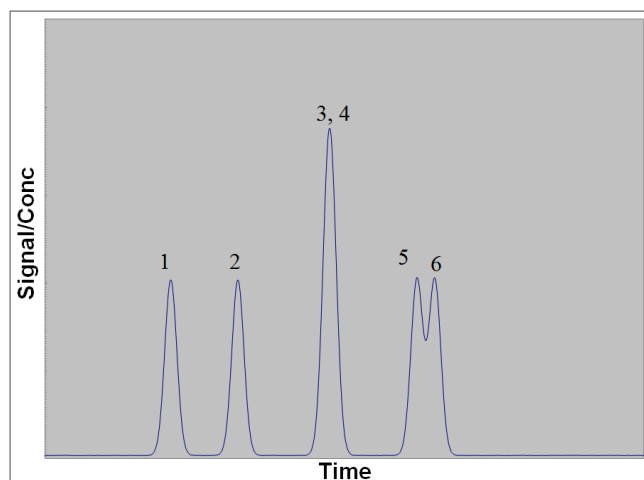*timothy.urness@drake.edu; phone 1515 271-2118; fax 1 515 271-2055

Figure 1. A simulated chromatogram of a mixture with six solutes. The X-axis is time. The Y-axis is the signal that is proportional to the amount of each compound present. Note solutes 3 and 4, (as well as 5 and 6) exit the system at the same time, making it impossible to identify and quantify the presence of each compound.

A problem occurs, however, when two different compounds exit the column at the same time. In Figure 1, the components 3 and 4 (and 5 and 6) did not separate using a particular combination of column and solvent. (The combination of a column and solvent is hereafter termed "system.") To get these components separated, a different chromatographic system is necessary. However, there are hundreds of different chromatography systems available with a wide range of interaction abilities. Therefore, it is highly desirable to classify the properties of the systems in order to make easy comparisons between them. Systems with similar properties will likely produce similar separations, whereas systems that are chemically different may lead to more effective separations. In this way, a second analysis can be done using a different chromatography system that is more likely to produce the desired result.

2.2 Retention Models

Retention models, such as linear solvation energy relationships (LSERs) [1] and the hydrophobic subtraction model (HSM) [2], use large variegated sets of solutes to quantify the contributions of specific intermolecular interactions to retention. Both models represent these contributions using a set of five distinct parameters, with each parameter reflecting a different chemical property of the chromatography system being studied. A general HSM equation is shown below

$$R = \eta'H - \sigma'S^* + \beta'A + \alpha'B + \kappa'C$$

where R represents measured retention data for a variety of solutes of varying η', σ', β', α', and κ' values. These variables relate to different characteristics of the solutes. The corresponding parameters, H, S*, A, B, and C, represent properties of the chromatographic system and are determined through multi-parameter linear least squares regression. The LSER is similar in design but uses different input parameters. Mathematically, however, both models can be dealt with using identical methodologies for the analyses we present in the manuscript.

Hundreds of chromatography systems have been characterized using LSERs and the HSM and the resulting parameters are available in the literature [2, 3]. We have developed a way to use the information contained in the LSER and HSM parameters to compare the chemical properties of different chromatography systems. Traditionally, the ratio of each coefficient to the H-coefficient is calculated within each HSM equation (the v-coefficient is used in the LSER model) [4]. This results in four distinct ratios (S*/H, A/H, B/H, and C/H) that characterize each system. Then we correlate the ratios for one system against those of a second system. These linear regressions result in statistical parameters that characterize the correlation, including the slope, intercept, and the square of the correlation coefficient (r^2). Correlations resulting in a slope = 1.00, intercept = 0.00, and r^2 = 1.00 (from here on referred to as the 1,0,1-point) indicate strongly correlated systems that would give very similar separations, and in some cases, identical separations. Figure 2 illustrates how systems can be compared using these statistical parameters. The Discovery C18 system is compared against two

different systems: another C18 system, the XBridge C18, and a system with an embedded polar group, the Symmetry Shield C18. Clearly, the Discovery and Symmetry system parameters are poorly correlated, meaning that the Discovery and Symmetry systems interact differently with a range of solutes. Because of this difference, solutes that are not separated using one system (e.g. Discovery) may likely be separated by the other (Symmetry). Conversely, the Discovery and XBridge systems are highly correlated with a slope close to 1.0 and an intercept close to 0.0. These two systems are chemically similar. Therefore, they interact with solutes in similar ways and likely produce comparable separations. Thus, if the Discovery system is not achieving a desired separation of compounds in a mixture, it is unlikely that switching to the XBridge system will improve the separation.
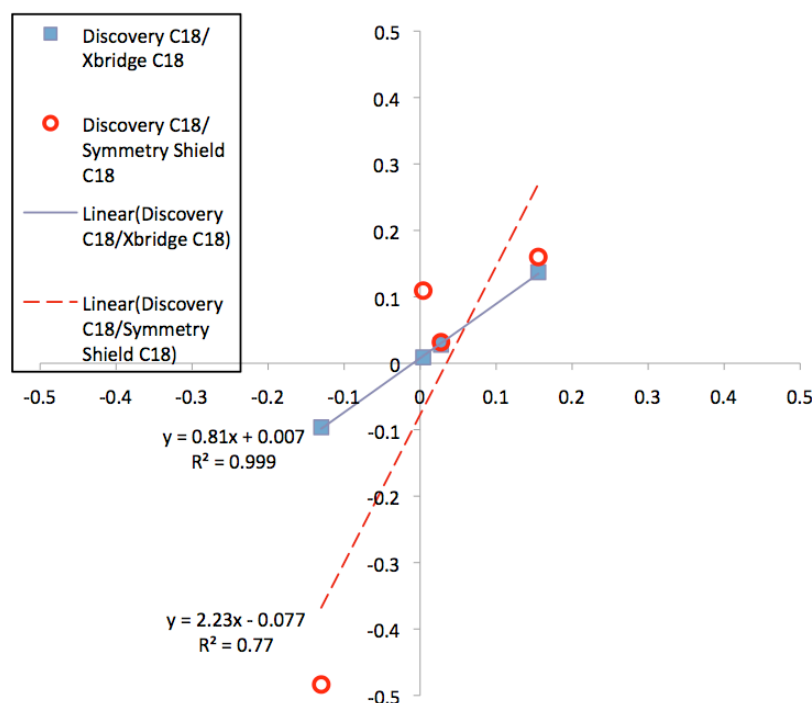

Figure 2. A plot of the correlation of the XBridge C18 and Symmetry Shield C18 systems versus the Discovery C18 system. The axes are defined as retention model HSM coefficient ratios. The XBridge and Discovery systems (■) are highly correlated with a slope close to 1.0 and an intercept close to 0.0. Conversely, the Symmetry and Discovery system (○) ratios are poorly correlated.

Such comparisons are useful, but still only allow for the analysis of two systems at a time. Below we introduce a data set that contains 372 chromatography systems [5]. This leads to 69,006 unique comparisons, each characterized by a slope, intercept, and r^2 value. In addition, the ratio of the two systems' HSM H-coefficients (v-coefficients when using the LSER) can indicate when two systems will produce not just similar, but identical separations. Thus, each comparison contains four data values (slope, intercept, r^2, and H (or v)-ratio), meaning that 276,024 individual numbers result from an analysis of that data set. Data sets as large as 450 systems, resulting in over 400,000 individual numbers are available in the literature [5]. The challenge, therefore, is to create visualization methods that allow facile comparisons between systems without having to sift through spreadsheets of data to extract the information that can guide analysts in their selections of chromatography systems. The visualization system presented below provides a way to quickly and easily select chromatography systems based on their similarities or differences.

3. APPROACHES TO MULTIVARIATE VISUALIZATION

One of the most challenging aspects of multivariate visualization is representing the data that enables each variable to be analyzed both individually and in the context of other variables. There are several different strategies for assigning data components to visual information-carrying variables [6]. In the following section, we describe three different methods for representing multivariate components of chromatographic systems.

3.1 Glyphs

A glyph is a graphical object designed to convey multiple data values. There is a rich body of research on effective glyph design as there are many attributes that can be applied to glyphs to represent multivariate data [7, 8]. For example, the use of color, size, shape, and orientation of glyphs can be used to represent a data element [6, 9]. A whisker or fan glyph, similar to a star glyph, uses the length of a ray from the center to indicate the magnitude of a variable [6, 10]. Arrows or Hedgehog plots also use the size, shape, orientation, and length of directed lines to represent variable components [11, 12]. In section 4.1, we demonstrate the use of these basic techniques in developing a scatter plot for the visualization of multiple variables of systems in a 3D environment.

Advantages of using glyphs to represent multivariate data include that they are often simple and intuitive. A glyph has many different options for representing multivariate data, but the perception of these attributes may vary (e.g., the perception of length is superior to the perception of color or orientation) [13]. Disadvantages also include the complexities involved with representing a large amount of data (clutter) and the accurate perception of the multiple variables each glyph is designed to convey.

3.2 Selectivity Triangles

In the analysis of chromatography systems, Fu and Khaledi used a plot referred to as a "selectivity triangle" to characterize and classify chromatography systems [14]. A selectivity triangle is a chart in which three different LSER coefficient ratios are aligned on the sides of an equilateral triangle [15, 16]. A data point (i.e., chromatography system) is normalized according to the three parameters and plotted within the area of the triangle. Systems that are close to each other in the triangle should generally exhibit similar chemical properties (see Figure 3).

Selectivity triangles are simple and intuitive to use, and chemists are familiar with reading them. However, they are only able to represent three parameters, when more are often used in retention models. Furthermore, the clustering of groups within selectivity triangles can be misleading [17]. Additionally, when the number of systems gets large, it is difficult to visualize all of the discrete points (see Figure 4), and the triangles are difficult to manipulate if one wants to focus on specific areas of the graph.
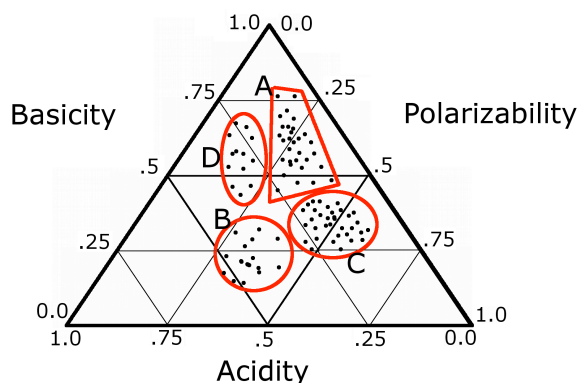

Figure 3. An example of a selectivity triangle that simulates the comparison of 70 different chromatography systems. Systems that are close to each other should generally exhibit similar properties. In this case, four groups (labeled A,B,C,D) are identified in the selectivity triangle.
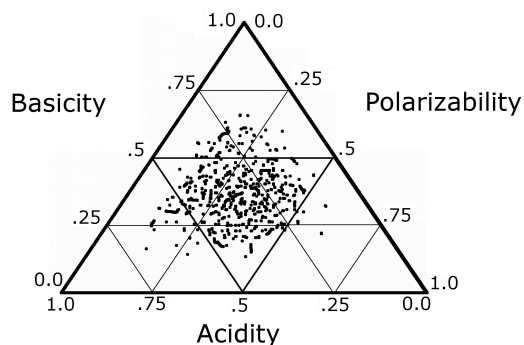
Figure 4. A selectivity triangle representing 366 chromatographic systems. With the exception of the extreme outliers, it is difficult to identify individual points, making it difficult to compare specific systems to one another.

3.3 Parallel Coordinates

Parallel coordinates is a visualization technique that represents a data dimension with a vertical (or horizontal) axis. Information for each multi-dimensional data point is represented by a poly-line that traverses all of the axes. The poly-line intersects each axis at a position proportional to its value. An advantage of this system is that the number of dimensions that can be represented is limited only by the resolution of a display device. Another advantage is that the point of intersection of the poly-line with each axis is easy to quantify. Disadvantages, however, include a potential for unintended biases caused by the order of axes and the analysis of data trends when numerous values are plotted (Figure 5) [19]. Additionally, as the distance from one data element to another is of primary importance in our application, comparing relative distances from one record to another can be challenging.
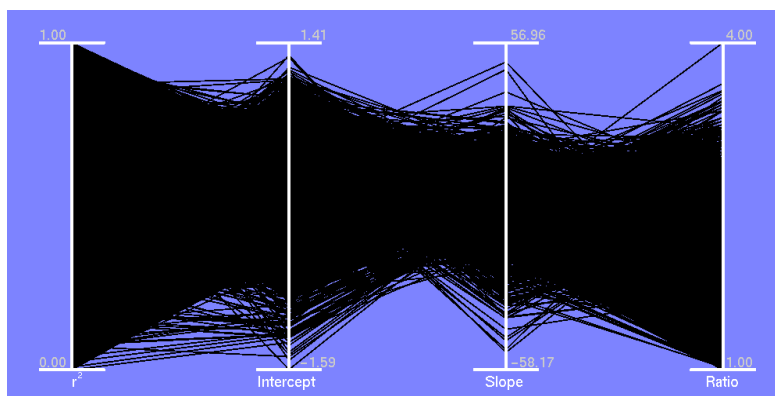

Figure 5. A parallel coordinates display of 372 systems that yields 69,006 comparisons. Note that the perception of specific systems or data trends is difficult due to the amount of over-plotting.

4. VISUALIZATION OF CHROMATOGRAPHIC SYSTEMS

The goal of our visualization system is to easily analyze the similarities and differences between chromatography systems. We have developed side-by-side visualizations that represent the same data (scatter plot with specialized glyphs alongside parallel coordinates) that are controlled by a graphical user interface. The simultaneous visualizations allow chemists to use the most appropriate visualization technique to best interpret the data.

4.1 System Selectivity Cube

We create a 3D scatter plot [20] that utilizes similar concepts as the familiar selectivity triangle (section 3.2) with the goal of identifying similar and different chromatography systems. To reflect this similarity, we have named this visualization tool the "System Selectivity Cube," or SSC.

A 3D scatter plot of the data for *n* systems is created as follows: the coefficient ratios from the HSM (or LSER) equation of system 1 (the first system in the list) are correlated against those for system 2. The first system is then compared to each of the following systems 3 through *n*. Next, the second system is correlated against systems 3 through *n*. This is continued through the data set and ensures that the comparison of two systems is plotted only once. The corresponding slope, intercept, and r^2 values for each correlation are plotted as a sphere in a 3D cube. Thus, the correlation between two systems is defined on a 3D Cartesian coordinate system (slope, intercept, r^2). To help in the perception of distance and location in the 3D environment, the user has control of viewing the SSC from any angle as rotation, translation, and zoom are controlled with a mouse. The color of each sphere can be used to delineate a fourth attribute.

The 1,0,1-point (represented in the SSC with a green sphere) represents two systems that are highly correlated and would produce quite similar separations. Thus, any glyphs in close proximity to this point represent systems that are likely to separate the components in a mixture in a similar fashion. Glyphs that are far distances from this point represent systems that are more likely to produce changes in the separation and thus offer alternate chromatographic results. Both results are useful. Similar systems can be used as replacements when systems are discontinued, and dissimilar systems can be used when the current system does not produce the desired separation.
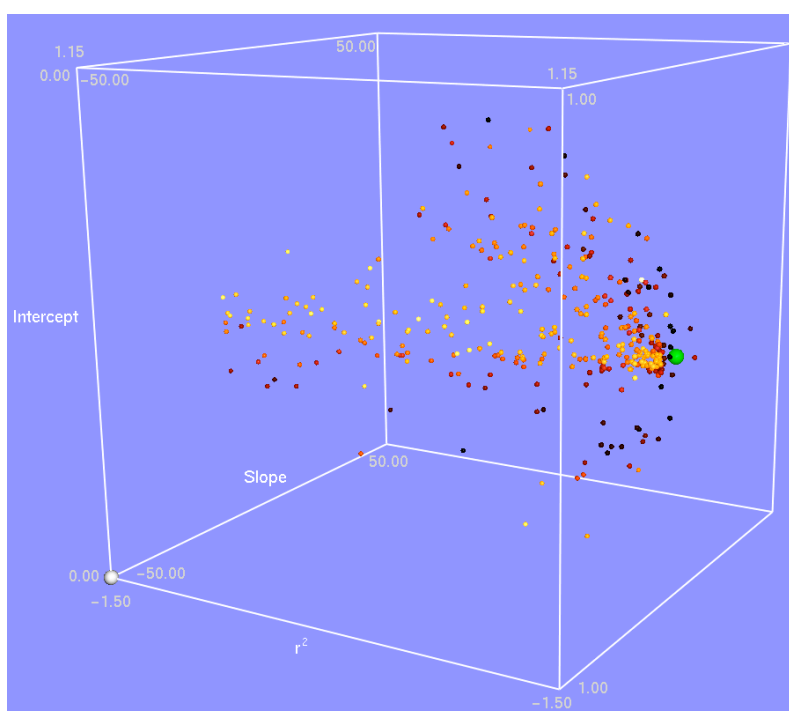

Figure 6. The System Selectivity Cube scatter plot. The parameters of approximately 300 chromatography systems are being compared to the Kromasil KR60-KCN chromatography system. The glyphs are colored according to a heated-object colormap representing the H-ratio. The large, green spherical glyph represents the 1,0,1-point.

When the correlation between parameter ratios produces a slope = 1.00, intercept = 0.00, r^2 = 1.00, *and* both system have the same H-coefficient (i.e., the ratio of the H-coefficients for the two systems being compared equals 1.00), two systems will produce not just similar, but virtually identical separations. As an alternative to using color to encode the H-ratio, we project the H-ratio onto the glyph by adding "spikes." Similar in principle to whisker, fan, or star glyphs [8, 10], the length of the spikes indicates the magnitude of the H-ratio, with spherical glyphs representing a ratio of 1.0. Thus, if a glyph is in close proximity to slope = 1.00, intercept = 0.00, and r^2 = 1.00, *and* exhibits very short spikes, then the two systems produce virtually identical separations. The H-ratio is computed such that the lowest volume coefficient is used in the denominator, ensuring the ratio is always greater than or equal to 1.0 (Figure 7).
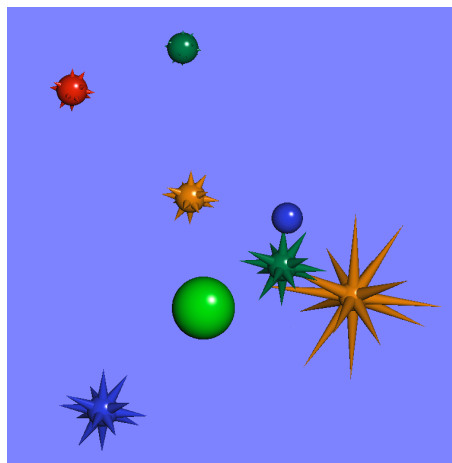
Figure 7. Specialized glyphs allow for a more detailed analysis of the SSC. The length of the spikes corresponds to H-ratio magnitude. The large light-green sphere corresponds to the 1,0,1-point. Color corresponds to the different selectivity triangle groups described in section 3.2. The spherical blue glyph in close proximity to the 1,0,1-point indicates a system comparison that would produce virtually identical chromatograms.

4.2 Parallel Coordinates

In addition to the SSC scatter plot, we simultaneously supply a window that visualizes the data using parallel coordinates. The data generated by comparing the systems as described in section 4.1 are applied to a parallel coordinates visualization system. The system is constructed with four independent axes labeled r^2, intercept, slope, and (volume) ratio. The r^2, intercept, and slope correspond to the linear correlations of HSM or LSER equations as explained previously. The ratio corresponds to the ratio of the H (or v)-coefficients used in the linear correlation of two systems' HSM or LSER equations.
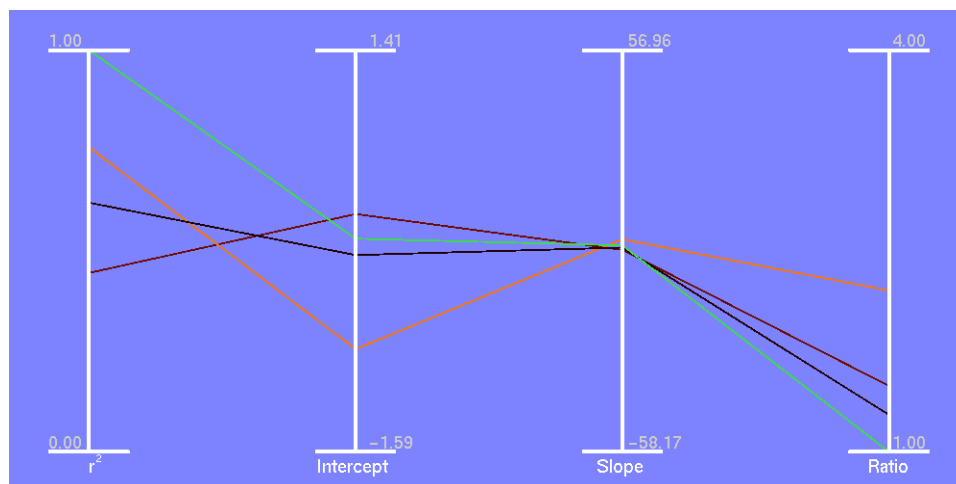
1.00	1.41	56.96	4.00
0.00	−1.59	−58.17	1.00
r^2	Intercept	Slope	Ratio

Figure 8. A parallel coordinates system that visualizes four different dimensions (r^2, intercept, slope, and H-ratio) of three systems. The green poly-line represents an ideal relationship (the 1,0,1-point and a H-ratio of 1.0).

Figure 8 demonstrates how parallel coordinates can be used for comparison of chromatography systems. The green poly-line represents the correlation where slope = 1.00, intercept = 0.00, r^2 = 1.00, and H-ratio = 1.00. The comparison of systems is represented as a poly-line in which the intersection of the poly-line with the axes indicates the appropriate value for each dimension. The colors of the poly-lines can be applied via a colormap to reinforce any of the dimensions. Alternatively, color can be applied according to the groupings of interest. For example, colors could be used to indicate comparisons of systems within in the same group specified by Fu and Khaledi [14].

The use of parallel coordinates has a few advantages over scatter plots for this application. In particular, chemists are able to focus on a specific data dimensions (axis) and accurately quantify values along the axis more simply when using parallel coordinates. For example, quantifying the H-ratio for a specific comparison on the parallel coordinates axes can yield a much more specific measurement than identifying a color of a glyph on a range of a colormap. However, the perception of distance, and correspondingly identifying relationships that would likely result in different chromatograms, give the SSC (scatter plot) an intrinsic value. Ultimately, displaying a side-by-side visualization of the SSC and parallel coordinates allows chemists to take advantage of each visualization technique where most appropriate.

4.3 User Interface

When numerous data points are to be represented, scatter plots, selectivity triangles, and parallel coordinates are all subject to over plotting and visual clutter – causing the perception of data trends, correlations, and anomalies to be difficult. The usefulness of the visualization system is greatly enhanced by the ability to rotate, translate, and zoom within the SSC, and highlight and cull data by interacting with a user interface. The user interface is designed to facilitate the analyses that are typically conducted when comparing chromatographic systems.

First, any dimension of the data can be adjusted to focus on values that have a desired range. For example, the default minimum r^2 value is 0.0 and default maximum r^2 value is 1.0. The user has the ability to cull all system pairs within any range of values. Thus, displaying all values with r^2 values between 0.99 and 1.0 requires only a mouse click to adjust the range of values displayed. Secondly, the color mapping can be chosen to correspond to any of the data dimensions: the distance to the 1,0,1-point, the groupings of Fu and Khaledi, the chemical makeup of the systems, price, or any other value the user assigns to each system.

An additional feature is the ability to visually compare one particular system to a strategically selected subset of the systems in both the SSC and parallel coordinates representation. It is possible that a chemist performed a separation with a particular system, which produced little separation amongst several solutes. By comparing the chromatography system used against a user-selected subset, an acceptable alternative system can be easily identified. Any glyph or poly-line in the system can be highlighted or focused using the user interface and the numerical correlation results for all systems displayed can be output with the press of a button.

5. APPLICATIONS AND ANALYSIS

To illustrate the types of conclusions that may be drawn from the visualization system as well as its practical application, we provide two examples. First, we discuss the appropriateness of groupings of system selectivity triangles. We follow this discussion with an analysis of chemical compositions of chromatography systems.

5.1 Selectivity Groupings

As previously mentioned, Fu and Khaledi proposed the use of a selectivity triangle to sort chromatography systems into four groups [14]. According to this theory, systems that cluster in the selectivity triangles should produce similar selectivities. Therefore, systems from the same group, when correlated to one another, should be plotted close to the 1,0,1-point in the SSC. In many cases, this behavior occurs as expected (Figure 9). However, there are some cases in which some systems within the same group do not correlate as expected. This is particularly true of systems in group B (Figure 10). Group B contains some sodium dodecyl sulfate (SDS) systems and some lithium perfluorooctanesulfonate (LiPFOS) systems. The comparisons between SDS and LiPFOS systems generally plot at a greater distance from the 1,0,1-point. This suggests that perhaps systems in group B could be further divided into two subgroups.
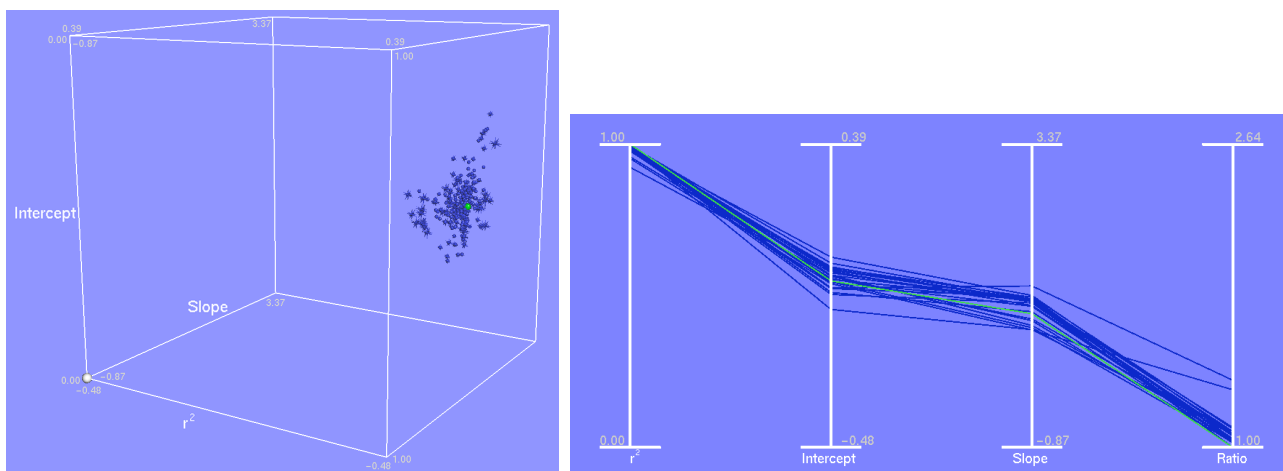
Figure 9. SSC (left) and parallel coordinates (right) depicting systems in Group A of reference [14]. Note that the data is clustered within a small range to the 1,0,1-point, which indicates that the systems are chemically similar.
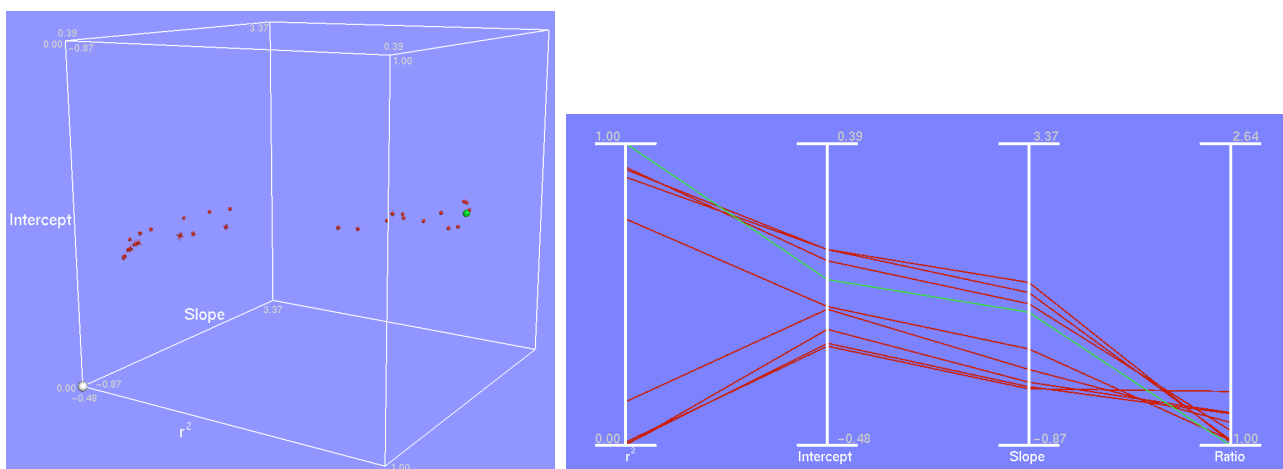

Figure 10. SSC (left) and parallel coordinates (right) depicting systems in Group B of reference [14]. Note that the data is not clustered near the 1,0,1-point, indicating that the systems are not similar.

5.2 Chemical Compositions of Chromatography Systems

The particles in chromatography systems can have many different chemical compositions. If we consider only those systems made from high purity silica, onto which chains of 18 carbon atoms are bonded to the surface, it would be expected that comparisons among such systems would be plotted near the 1,0,1-point. In fact, this is not the case. Figure 11 shows a SSC and accompanying parallel coordinates created by comparing the Discovery C18 system to twelve other high purity silica C18 systems.

Note that many of the glyphs are plotted in the 1,0,1-region of the SSC, indicating that those systems are similar to the Discovery C18 system. However, several systems are plotted a significant distance away. This analysis shows that even within a subset of systems that should possess similar characteristics based on their compositions, there exists substantial variation. The differences in these systems may be due to differences in manufacturing processes, but since much of that information is proprietary, it is difficult to specify the origins of these differences. These are not artifacts of this comparison method, as similar conclusions have been reached using other schemes [21].
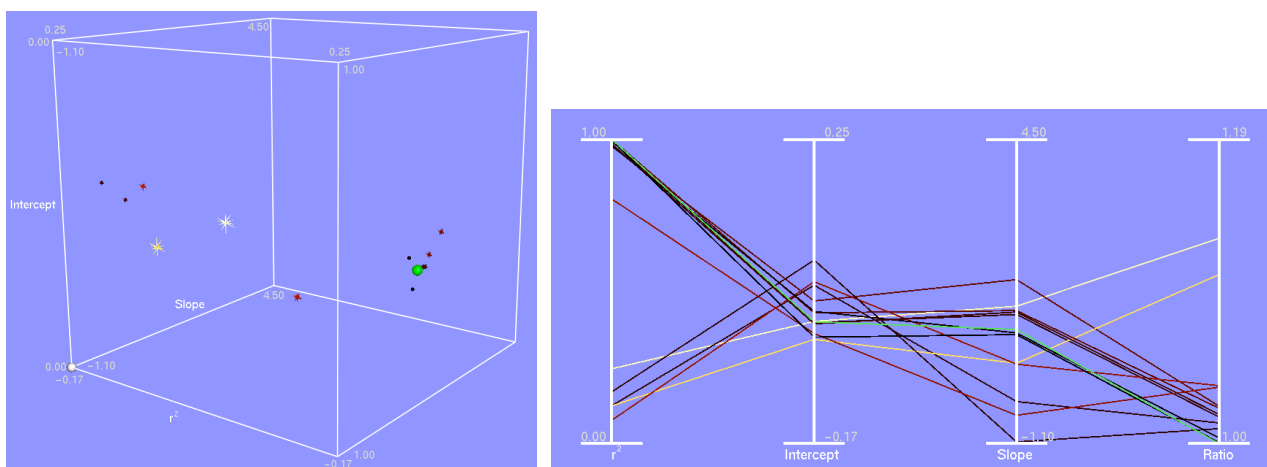
Figure 11. SSC (left) and parallel coordinates (right) of twelve C18 systems compared to the Discovery C18 system. Note that several of the systems compare closely to the Discovery C18 system (close to the 1,0,1-point marked by the green sphere or green poly-line), while others do not.

Table 1 shows the 12 systems that were compared to the Discovery C18 system. The final column of the table, distance, quantifies the normalized distance that system's comparison glyph was plotted from the 1,0,1-point. Higher numbers are farther away and more likely to provide different separations.

Table 1. Values of the HSM retention model for the twelve systems compared to the Discovery C18 system as displayed in Figure 12. Distance gives a metric to measure the similarity of each of the systems to Discovery C18 system.

Name	H	S	A	B	C (7.0)	Source	Distance
ACE 5 C18	0.999915	0.026527	-0.09635	-0.00651	0.096051	ACT	0.05
Halo-C18	1.106845	0.048397	0.006186	-0.04998	0.040148	Advanced Materials Technology	0.76
Zorbax StableBond 80A C18	0.996276	-0.03203	0.264318	-0.00126	1.041146	Agilent	0.92
Advantage Armor C18 120A	0.962	-0.014	-0.076	-0.004	0.261	Analytical Sales & Service	0.18
Ultrasphere ODS	1.085075	-0.01431	0.173439	0.067603	0.382106	Beckman	0.88
ProntoSIL 120 C18 H	1.005094	0.008264	-0.10584	-0.00428	0.155958	Bischoff	0.07
Epic C18	0.950437	-0.02668	-0.20334	-0.00655	-0.04073	ES Industries	0.94
Vydac Everest	0.992854	0.049019	0.121475	0.004048	0.340998	Grace-Vydac	0.93
Luna C18	1.017689	0.025221	0.072232	0.008397	-0.03602	Phenomenex	0.35
Discovery C18	0.983923	0.027291	-0.12823	0.003683	0.153263	Supelco	
Hypurity C18	0.980486	0.025148	-0.09063	0.002754	0.167441	Thermo/Hypersil	0.04
Pursuit C18	1.00146	0.003827	-0.1663	0.012338	0.226056	Varian	0.06
Xterra MS C18	0.984468	0.012432	-0.1426	-0.01488	0.050987	Waters	0.05

In practice, the information in this SSC could be used as follows: suppose that a separation on the Discovery C18 system was not successful (i.e., it contained overlapping peaks as in Figure 1). There may be dozens of available systems to choose from to replace it. In order to efficiently choose the system with the best chance of improving the separation, the SSC can be used. By comparing the Discovery C18 system to twelve other available C18 systems, those systems farthest away from the 1,0,1 point would be the most prudent choices for the next separation trial as they have the greatest potential to provide different (and hopefully successful) separations.

Alternately, when trying to replace a discontinued system with one that produces comparable separations, it would be wise to select systems represented by glyphs in close proximity to the 1,0,1-point with H-ratios close to 1.00. Systems with these properties represent chromatography systems that are almost identical, meaning that they would likely provide nearly identical separations.

6. CONCLUSION

We have created a 3D visualization system capable of comparing the chemical properties of chromatographic systems. The visualization system combines scatter plots, parallel coordinates, and specialized glyphs to assist in the analysis of chromatographic data and in comparisons of the numerous possible systems. Using this tool, literally hundreds of separation systems can be readily compared simultaneously – greatly facilitating the ability to select systems that are likely to produce desired separations during method development. Note that it is not only the classification of individual pairs of systems that is useful, but also the comparison of multiple systems to identify properties, structures, and the identity of pairs of systems with the greatest likelihood for differences in selectivity. The software is available at http://artsci.drake.edu/urness/download/ssc.html

ACKNOWLEDGEMENTS

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