Visual And Computational Analysis Of Structure-Activity Relationships In High-Throughput Screening Data

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Summary of Recent Advances

Novel analytic methods are required to assimilate the large volumes of structural and bioassay data generated by combinatorial chemistry and high-throughput screening programmes in the pharmaceutical and agrochemical industries. This paper reviews recent work in visualisation and data mining that can be used to develop structure-activity relationships from such chemical/biological datasets.

Keywords

Data analysis, data visualisation, data mining, drug-likeness, classification,

Introduction

The search for lead compounds in the pharmaceutical industry (and also in the agrochemical and related industries) has historically followed an inherently sequential process, in which individual compounds are synthesised and then tested for biological activity, with the results of such experiments being fed back to inform the selection of further molecules. Developments in combinatorial chemistry [1-5] and in high-throughput screening (HTS) [6-8] mean that such operations have been largely replaced by a massively parallel mode of processing, in which many thousands of molecules can be synthesised and tested at the same time. This has resulted in an explosion in the volume of data that is available for the identification of structure-activity relationships (SAR). Quantitative SARs, typically using physicochemical parameters or 3D molecular fields with statistical techniques such as multiple regression or principal components analysis, have been an important tool for medicinal chemists for many years. However, such methods are normally used for the detailed analysis of small numbers of structurally-related molecules, and are not applicable to the large, structurally heterogeneous datasets that characterise modern HTS systems. There is hence much current interest in novel soft-computing approaches that might be applicable to the analysis of such datasets, and we here review recent work in this area, focusing upon the use of visualisation and data mining techniques.

Visualisation Techniques

Information and data visualisation plays an important role in practically all areas of scientific research. Consequently, many visualisation techniques like scatter plots or histograms have been developed [9,10]. That these established, simple visualisation techniques can help to identify patterns also in large datasets is demonstrated nicely in an article by Hand *et al.* [11*]. However, very interesting developments have been made in information and data visualisation over the last years that are especially aimed at large datasets [12**,13]. A thorough introduction to this important field was recently published by Card *et al.* [12**], who provide a collection of important classic and cutting edge articles in this field.

With the increasing importance of high-throughput chemistry and screening, the consequent increase in data volume [14] requires more effective methods to visualise and structure data produced in research. In addition, the emerging consolidation of research data in chemical data warehouses [15] makes it now more feasible to mine these sources. However, only few applications in chemistry have appeared over the past years. It can however be expected that visualisation will have a major impact on drug discovery over the next years [16].

Two general purpose data visualisation programs will act as examples of what is currently possible. Spotfire [17,18] (Spotfire® is a product of Spotfire Inc., Cambridge, MA, USA) is probably one of the best-known data visualisation and mining programs. Although it only provides basic graphs like scatter-plots, histograms and pie charts, its special features like database connectivity and interactive query devices make it a powerful tool for interactive visualisation and information analysis (see Figure 1). Any change of the control elements is instantly executed and the user gets an immediate feedback. Another interesting visualisation program that has been applied to pharmaceutical research data is OmniViz Pro™ (OmniViz Pro is a trademark of OmniViz, Inc., Columbus, OH, USA). In contrast to Spotfire, this software is based on new methods for information visualisation developed by the *Information Visualisation* group of the *Pacific Northwest National Laboratory* (see http://multimedia.pnl.gov:2080/infoviz/). Figure 2 gives an example of the type of graphs that can be created with OmniViz Pro.

In many cases, the available data are multidimensional. This is especially true for chemical compounds that can numerically be represented either by fingerprints or a set of descriptor values. In order to explore multidimensional data, it is necessary to map the data points into a 2- or 3-dimensional space. This mapping is frequently called non-linear mapping. The aim of non-linear mapping is in most cases to preserve neighbouring properties, so that data points that are close together in the multidimensional space will be close together in the low-dimensional space. A variety of methods have been used over the last years in chemistry for the visualisation of databases [19], in diversity analysis [20,21] and for the analysis of structure-activity relationships [22,23].

An established method for non-linear mapping is multidimensional scaling [24]. Principal component analysis or singular value decomposition can be used to get an initial estimate for the low dimensional representation of data points. In a second step, this projection is improved by optimising the data point separation in the low-dimensional space so that they resemble the distances of the data points in the high-dimensional space better. The quality of the mapping is measured by using the Sammon's stress function or a variation thereof. Clark *et al.* [25*] proposed a particularly interesting modification of the original stress function. They observed that when mapping chemical structures based on fingerprints, the local similarity is not well preserved. This is due to the fact that the similarity measure used is an insufficient measure of dissimilarity. The suggested modification of the stress function ignores contributions of compounds with similarity smaller than a given value. The mapping obtained with the modified version clearly shows a more pronounced clustering of similar compounds.

Unfortunately, multidimensional scaling is not well suited for large datasets, as the method scales quadratically with the number of data points. A significant improvement compared to conventional methods was achieved by Xie *et al.* [26], who applied the truncated-Newton optimisation method to improve the initial mapping obtained from singular value decomposition. They were able to demonstrate that the truncated-Newton optimisation can be up to 100 times faster than using the steepest descent method for optimisation. The approach is however not suitable for sets of several thousand data points.

A variety of different approaches were used to apply neural nets for non-linear mapping. The advantage of neural nets is that they can be used to predict positions of new data points in the low-dimensional space. A number of studies have used self-organising maps [27*] to visualise and analyse the diversity of databases [19,22,23]. It is also possible to use a multi-layer back-propagation neural net with n input and m output neurons (m=2,3). The output of the neural net for each output can be used as its m lower-dimensional co-ordinates [28]. Izrailev and Agrafiotis modified this method [29*]. Instead of using the full dataset, they suggest to train a feed-forward neural network to learn the projection obtained from conventional non-linear mapping of a subset of all data. The trained network can subsequently be used to project the whole compounds set. In an example of a combinatorial

library containing 57498 compounds, a subset of only 100 compounds (0.2 %) was already sufficient to generate a reasonable map of the whole dataset. Another approach uses a neural net with *n* neurons in the input and output layer and several middle layers. One of the hidden layers has *m* neurons. The net is trained to reproduce the input variables at the output neurons. The reduced dimensionality representation of a compound can then be read out from the *m* neurons of the middle layer [30].

While the described non-linear mapping techniques try to preserve the neighbouring relationship, the generated map might not necessarily be the best mapping if the aim is to visualise a classification. The classification mapping methods proposed by Su *et al.* [31*] aim to achieve this. The examples demonstrate that the techniques are able to give a qualitative or semi-quantitative picture.

Probably the most important problem during lead optimisation in drug discovery is to determine SAR information. While it is quite feasible to develop this SAR knowledge for small numbers of compounds manually, it is necessary to automate this process for large datasets. The aim is to identify sets of similar compounds that have a common structure and show a systematic variation in one part (e.g. a substituent, a spacer or a ring system). Therefore, it may be interesting to compare one particular compound to a variety of other compounds in the dataset, to visualise the common features, and hence the potential pharmacophore patterns, that are present.

Sheridan and Miller looked at recurrent topological substructures [32*]. They compare the structures of pairs of compounds and determine all common, possibly disconnected substructures. These substructures are scored and the highest scoring common substructure determined. This approach allows identifying 2D pharmacophores for a set of compounds. Another approach based on maximum common substructures is used by Distill (Distill is a trademark of Tripos Inc., St. Louis, MO, USA). This program develops a hierarchical organisation of compounds using maximum common substructures. The approach is however limited by the fact that there is only one classification tree for the structures created. This means that only one of all possible groupings of compounds can be explored, which will limit the SAR information that could be extracted from a set of compounds. Instead of using only a tree, the program LeadPharmer (LeadPharmer is a trademark of BioReason

Inc., Santa Fe, NM, USA) constructs ‘phylogenetic-like groupings’ of possible substructures [33-35]. The term ‘phylogenetic-like groupings’ was chosen to indicate that substructures are related. The determined substructures are used to assign compounds to different classes. It is possible that a compound can be assigned to more than one class. Using available activity information, interesting classes can be identified and the effect of structural variations on activity studied.

One drawback of the approaches mentioned so far is that the construction of the tree classification can be a quite time-consuming process. The program LeadScope (LeadScope is a trademark of LeadScope Inc., Columbus, OH, USA) tries a different approach [36*]. The program does not construct possible substructures for a number of given compounds, but uses a set of predefined structure fragments (large taxonomy of familiar structural features such as functional groups, aromatics, and heterocycles) to classify the compounds. Therefore, compounds can be assigned to more than one group depending on the structural fragments they contain. The compound classification can be used to explore structure activity relationships in a dataset and search other databases for related structures (see Figure 3).

Data Mining Techniques

Visualisation enables a chemist to interact directly with sets of compounds, but can prove difficult when very many data points need to be considered. Data mining methods, which seek to identify meaningful inter-variable relationships in large, multidimensional datasets, are now being used in a wide range of subject domains, and it is hardly surprising that several of these methods have been used to investigate SARs. Three good general sources on data mining methods are the KDNUGGETS Web site (see URL http://www.kdnuggets.com), and the classic texts by Mitchell [37*] and by Duda and Hart [38*]. The basic problem addressed by all of these methods is that of classification: given a set of molecules for which the activity (or inactivity) is known (the training set), derive a rule that will enable new molecules (the test set) to be classified into the predicted-active or predicted-inactive classes. Training data can be generated internally from ongoing lead-discovery programmes or from publicly available files such as the *MACCS Drug Data Report* (MDDR), *Available Chemicals Directory* (ACD) and *Standard Drug File* databases; the resulting classifications can then be used to

guide the selection of new molecules for synthesis and testing. Thus far, chemical applications have involved the following principal approaches: statistical criteria, decision trees and neural networks.

Medicinal chemists have known for many years that certain types of molecule are unlikely to possess the characteristics necessary for a successful drug: they may be too large to pass the blood-brain barrier, they may be insoluble, they may contain toxic or highly reactive functionality, *etc.* Attempts to quantify such characteristics started with Lipinski's 'Rule of Five' and there have been several, more recent statistical analyses of sets of drug molecules (e.g., [39,40,41*]). A more sophisticated mode of analysis considers also sets of non-drug (or, more usually, presumed non-drug) molecules, this allowing the identification of rules that can be used to assess the 'drug-likeness' or 'drugability' of molecules. An obvious starting point is the distribution of global molecular properties in sets of drug and non-drug molecules. This approach was first studied by Gillet *et al.* [42**], using the distributions of molecular weight, numbers of rotatable bonds, numbers of aromatic rings and of hydrogen bond donors and acceptors, CLOGP and the ${}^{2}K_{\alpha}$ shape index. Here, the distributions for the value of some property in the drug and non-drug molecules is processed by a genetic algorithm (GA) [43] to produce a bioactivity profile, a set of weights that maximise the separation between the distributions for the two classes of molecule; the profiles, are then applied to the property values for test-set compounds so as to obtain a ranking of them in decreasing order of predicted drug-likeness. Gillet *et al.* subsequently described the use of the profiles in a GA for selecting combinatorial libraries of structurally diverse, drug-like molecules [44]; an analogous compound selection procedure has been reported by Sadowski [45] and there is now an extensive literature on the inclusion of drug-likeness in library design procedures [46-49]. A very similar set of global molecular properties has been studied by Oprea in a detailed analysis of several publicly-available datasets [50**], this analysis resulting in the specification of rules for compound-selection that are noticeably more precise than the original Rule of Five.

Statistical analyses of the presence of fragment substructures in active and inactive molecules provides a simple, and convenient alternative to the use of property information. Such approaches were first described almost three decades ago but current requirements for effective compound-selection

procedures has resulted in a surge of interest (se, e.g., [36*,51-53]). Similar approaches can be used to highlight substructures that are undesirable for drug activity (e.g., on grounds of toxicity or unwanted reactivity) [41*,54*].

Neural networks have been applied to a wide range of chemical problems [55**] and they were one of the first such techniques to be applied to drugability studies, the two papers by Ajay *et al*. [56**] and by Sadowski and Kubinyi [57**] appearing contemporaneously with the GA-based approach of Gillet *et al*. [42**]. Here, the network is trained using sets of drugs and non-drugs, and a scoring threshold derived that can maximally discriminate between the two classes; test molecules can then be classified by calculating the score when they are presented to the network. Work in this area is exemplified by the recent study of Frimurer *et al*. [58*]. These authors used sets of molecules from the MDDR and ACD databases to exemplify drugs and non-drugs, with each molecule represented by normalised counts of the numbers of CONCORD atom-types present. These representations were input to a multilayered feed-forward neural network which, after appropriate training, was able to achieve a success rate of 88% in classifying MDDR and ACD compounds that had not been involved in the training; importantly, when used in a predictive manner, the network was able to identify drug-like molecules noticeably different from those obtained from conventional 2D similarity searches. Sadowski discusses the use of a similar neural-network system to discriminate between crop-protecting and non crop-protecting compounds [45].

Decision trees provide an alternative classification tool. Here, the root of the tree represents an entire dataset, and this is subdivided into two (or more) subsets depending on the value of some splitting criterion. Various types of criteria can be used, such as the presence or absence of a particular substructural feature or a CLOGP value lying within a particular range. The potential splitting criteria are scored in some way, and the most advantageous chosen to split the dataset; the procedure is then repeated on the resulting sub-sets, and continued until some termination condition is satisfied. Several different splitting criteria and scoring schemes have been described [37*]. Decision trees were first used in drugability studies by Ajay *et al*. [56**]: these authors used the well-known C4.5 program (which employs an entropy-based scoring function) but who found that the resulting trees performed

less well than neural networks. More recently, however, Wagener and van Geerestein [59**] have used the successor program, C5.0, to distinguish between drug and non-drug compounds with a substantial measure of success on both public and corporate datasets. The most widely-used decision tree procedure for chemical applications has been the recursive partitioning approach, which uses a modified *t*-test for scoring potential splits. This approach has been popularised by Rusinko and co-workers, who have used it not only to analyse 2D fragment substructural data [60**] but also to suggest 3D pharmacophores [61,62]. Other recent examples of the use of recursive partitioning are provided by Cho *et al.* [63] and by Miller [64*]. Decision trees have the advantage over neural networks that they provide explicit, readily comprehensible sets of rules for discussion with medicinal chemists [59**], although Walters and Murcko believe that they are susceptible to over-training, producing classification rules with little predictive power [65]. Mello and Brown [66] have criticised them for assigning test data to just a single class, and have thus developed a hybrid approach that uses the feature-selection capabilities of recursive partitioning as the input to a Bayesian inference network, while Miller has combined recursive partitioning with *k*-nearest neighbour searching [64*]. Finally, Jones-Hertzog *et al.* [67*] describe the use of recursive partitioning to support a sequential HTS analysis of 14 G-protein-coupled receptor targets; other examples of data mining in sequential screening programmes are described by Stanton *et al.* [68] and Engels *et al.* [69*], using nearest neighbour and cluster analysis.

Drugability-based filtering is now common. That said, it must be emphasised that such schemes are still at a very early stage of development: they can often provide erroneous classifications if used without care [70], and they are arguably focused too much on known drugs rather than on the lead compounds that are the principal outputs of screening programmes [71*]. In addition, many of the reported studies thus far have focused on the difference between drugs and nondrugs; however, the same basic techniques can often be applied to the analysis of molecules from a particular therapeutic class if required [39,44,53,58*,72].

Conclusions

This brief review has highlighted some of the soft computing methods that are now being applied to the analysis of the structure-activity relationships present in HTS datasets. However, there are many other methods that have already been, or could be, applied to such problems: examples include ant-based computation [73,74], evolutionary Kohonen networks [27*], fuzzy clustering [23], support vector machines [75] and Bayesian learning [66]. We believe that methods such as these will prove invaluable in the analysis of the huge volumes of data that characterise modern pharmaceutical research, particularly when used in combination [76**.77**].

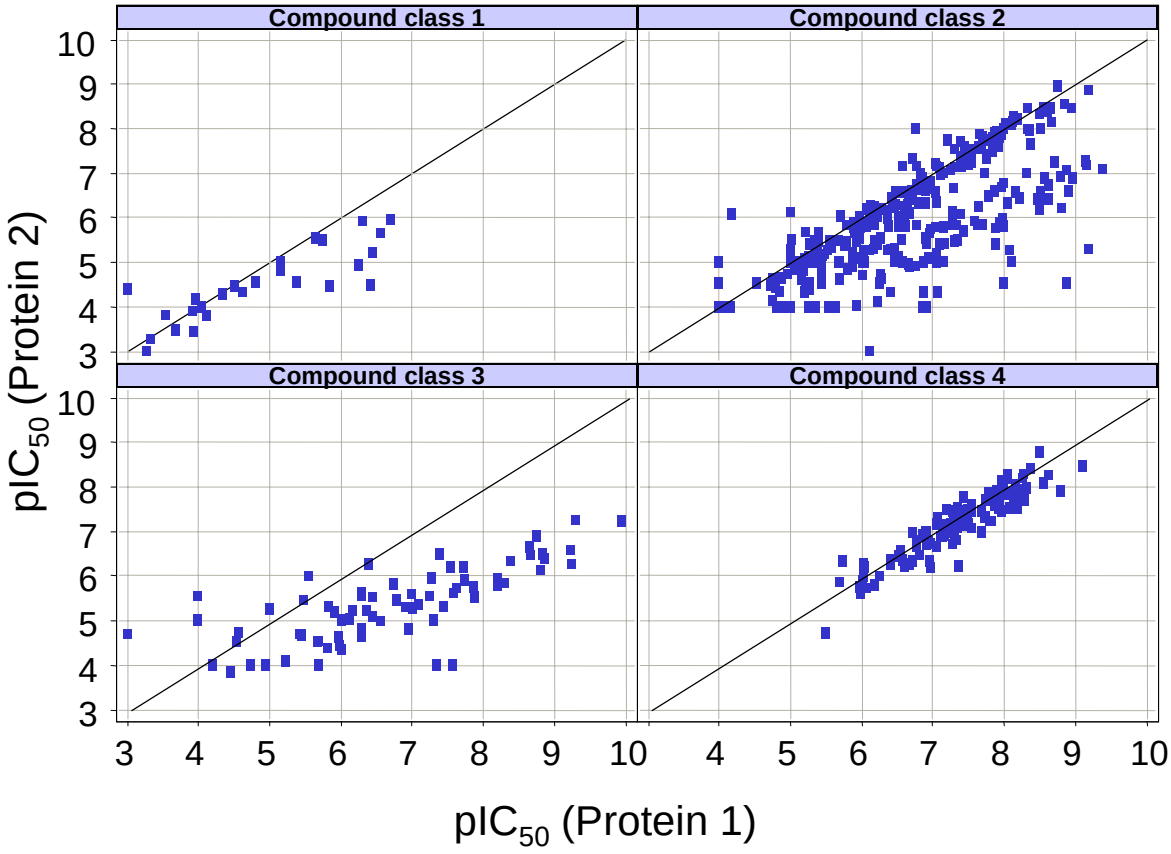
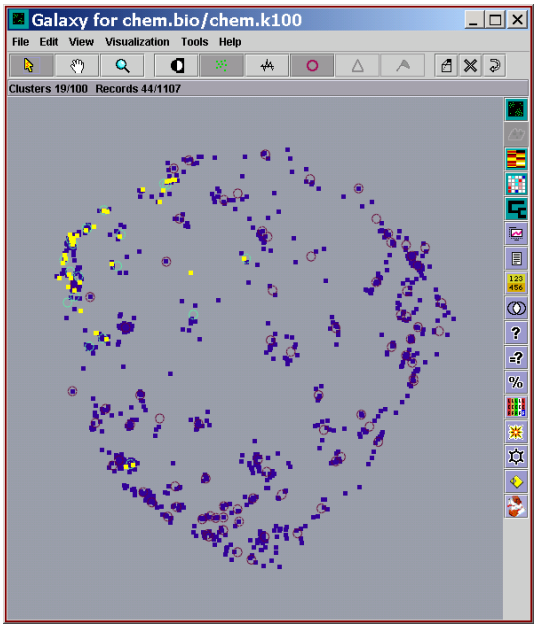


Figure 1: A trellis display created using Spotfire. The four scatter plots compare activity data of compounds measured for two subtypes of a protein. In addition, the compounds were classified into four different structural classes. Each scatter plot shows the data points for one structural class. A comparison of the different scatter plots reveals interesting details. The compounds in class 3 are more selective for protein 1, whereas the compounds in class 4 are equipotent on both proteins. Compound class 2 shows no preference but two groups of compounds are clearly visible. A comparison of the structures in the different classes can reveal further information about the SAR.

a) 

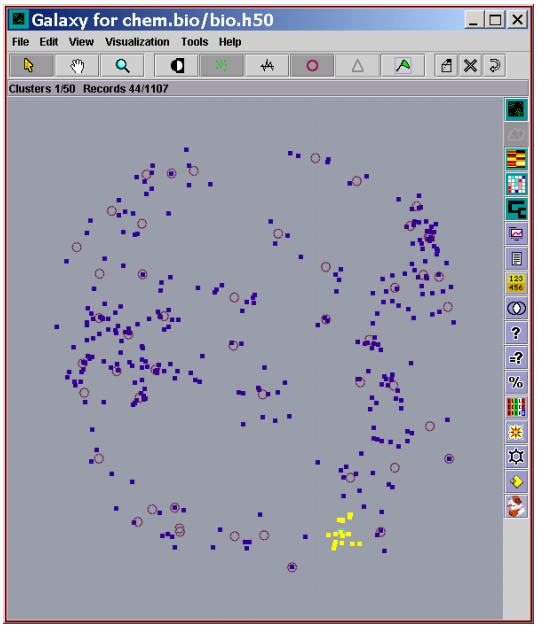
b) 

Figure 2: OmniViz Pro™, from OmniViz, Inc. (Columbus, OH, USA) provides integrated analysis of text, numeric, categorical, and genomic sequence data within a visual Cognitive Analytical Environment™. Here, the software was used in an analysis of 1107 compounds with defined fingerprints that had been screened in 19 biological assays.

In (a), the compounds are represented in a Galaxy™ view, a proximity map that shows how every record is related to every other record. In this map, the similarity is based on the fingerprints, providing a view of the chemical information space. Individual records (blue dots) represent each compound and the clusters of related compounds are evident (marked by circles). A separate Galaxy view in (b) shows the same compounds but with the similarity based on the biological activity profile (biological activity space). A cluster of compounds (lower right) was selected (highlighted yellow) in the biological activity space and the corresponding compounds were automatically highlighted in the structure-based Galaxy. The distribution of the compounds in the structure space indicates that most have similar fingerprint attributes (since they are located in close proximity), but a few are distant (e.g., two in the cluster at the bottom left). This suggests that an alternative set of structural attributes might create the same activity profile - suggesting a new class of structures to pursue.

Courtesy of OmniViz Inc.

Figure 3: The screenshot of the LeadScope user interface shows a comparison of two projects in the histogram view. The left panel shows the structural feature hierarchy open to reveal a portion of the Heterocycles:quinoline branch with quinoline, 2-phenyl selected. The central graphic panel shows parallel histograms comparing the contents of two projects relative to the structural features; each histogram bar gives the frequency of the feature class plotted on a log scale. The right panel contains a series of the property filters, which can be adjusted to select compounds with properties in specific ranges.

The database corresponding to the histogram on the left are compounds tested by the National Cancer Institute's (NCI) Developmental Therapeutics Program for growth inhibition and cytotoxicity against a panel of 60 human cancer cell lines. The comparison database – corresponding to the histogram on the right – are compounds available from Maybridge Chemical Company Ltd [Trevillett, Tintagel, Cornwall PL34 OHW UK].

Histogram bars are colour-coded based on the difference, expressed in number of standard deviations, between the mean activity of the subset of compounds containing a structural feature from the mean activity of the full set. In this example, IC50 data for the SF-295 cell line from the CNS panel is used for the NCI dataset. This technique can be used to locate subsets with unusually high mean activity and then identify new members of the structural class available from a commercial source.

Courtesy of LeadScope Inc.

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