Molecular Structure Similarity in the Context of Orphan Drug Legislation

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Introduction

An orphan drug is a medicinal product that is intended for the treatment of a rare disease that affects only a small number of patients, e.g., five in ten-thousand. According to the current European orphan drug legislation [a], the Community and the Member States shall not, for a period of 10 years, accept another orphan medicinal product, or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.[a, b] Thus far, the European Medicines Agency, the regulatory authority, has used human judgments of similarity when assessing new medicines for rare diseases. The similarity of a medicine product is evaluated taking into account the following three components of similarity: [b, c, d]

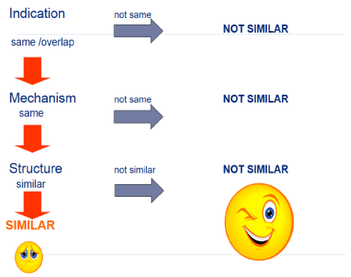


Figure 1 - Assessment of similarity in the context of the orphan drug legislation

Objective – Use of chemoinformatics in the evaluation of new medicines

Development of a mathematical model to predict similarity to support the evaluation of molecular structural similarity in the context of the orphan drug legislation.

Sample – One hundred pairs of active substances – Drug Bank 3.0

The sample contains 100 pairs of active substances. These pairs were selected randomly from among 1,140,624 pairs of molecules extracted from Drug Bank 3.0, for which the Tanimoto coefficient was calculated. The active substances selected belong to 42 different pharmacological groups.

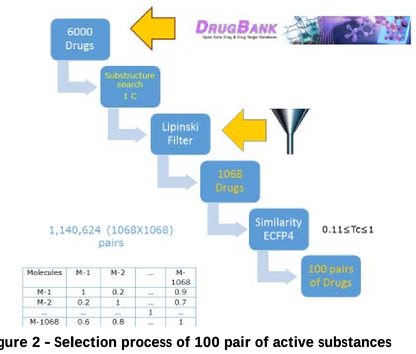


Figure 2 - Selection process of 100 pair of active substances

Experts

In this research project 143 quality experts from Europe, America and Asia with experience in assessing medicines participated in a survey on structural similarity. The experts were asked to decide the degree of similarity between the 100 pairs of active substances. These results were compared with the Tanimoto similarly coefficients using the following descriptors: ECFP4 (1024), ECFC4 (1024), Daylight (2048), Unity (988), BCI (1052), MDL (166), Extended (1024), Standard (1024), Estate (79), PubChem (881), MACCS (166), Morgan (2^{32}), Feat Morgan (2^{32}), Atom Pair, Torsion, RDKit, Avelon (2048), Layers (2048) and 1D descriptors (23 different descriptors characterising molecular properties).

Experimental work

Pipeline Pilot and KNIME protocols were set up for each different type of descriptor to calculate the similarity coefficient between each pair of active substances. In all protocols an Excel reader was used to read an Excel file containing the SMILES for each active substance. The respective binary descriptors were then generated for all compounds, and a script was used to compare each pair of compounds.

Results

The results of the questionnaires show that 51% of the pairs of molecules were classified as being not similar by the experts and the remaining 49% were classified as similar. These results reveal also that the experts are not in agreement concerning the similarity or dissimilarity of certain pairs of molecules. The levels of disagreement are due to the inherently subjective nature of similarity with an individual's perception that two objects are similar depending on a range of factors (such as their state of mind, gender, ethnicity, age, background and context, etc).

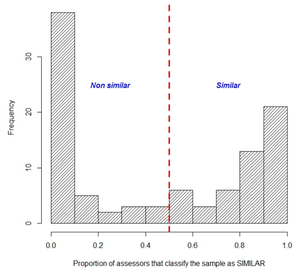
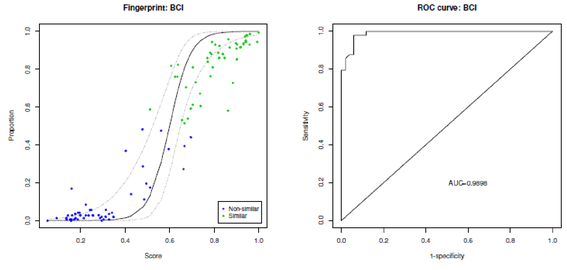


Figure 3 – Distribution of expert assessments

Logistic regression analyses demonstrated a strong relationship between the human and computed similarity assessments, with the resulting models having significant predictive power in experiments using previous judgements of similarity by the European Medicines Agency (EMA). The resulting regression models were then validated using a separate test-set containing 100 pairs of molecules that had previously been considered as orphan drugs.



$$logit\left(\frac{p}{1-p}\right) = -12.7578 + 2.1276x \leftrightarrow p = \frac{e^{-12.7578+2.1276x}}{1+e^{-12.7578+2.1276x}}$$

Figure 4– Mathematical model to assess similarity - Logistic regression

Table 1– Summary of the overall measures of the performance of the logistic regression for each fingerprint

Fingerprint	TROC	Predicted probability	Sensitivity	Specificity	Precision	Accuracy
ECFP4	0.490	0.406	0.980	0.922	0.923	0.950
ECFC4	0.364	0.415	0.980	0.882	0.889	0.930
Daylight	0.510	0.225	1.000	0.882	0.891	0.940
Unity	0.639	0.537	0.938	0.961	0.957	0.950
BCI	0.606	0.534	0.980	0.941	0.941	0.960
MDL	0.650	0.487	0.939	0.882	0.885	0.910
Tanimoto 1D	0.203	0.408	0.776	0.902	0.884	0.840
	0.185	0.379	0.816	0.863	0.851	0.840
Extended	0.610	0.694	0.959	0.961	0.959	0.960
Standard	0.587	0.593	0.959	0.941	0.940	0.950
EState	0.714	0.472	0.898	0.824	0.830	0.860
PubChem	0.776	0.618	0.878	0.922	0.915	0.900
MACCS	0.750	0.805	0.857	0.980	0.977	0.920
	0.656	0.525	0.939	0.902	0.902	0.920
Morgan	0.293	0.160	1.000	0.863	0.875	0.930
	0.400	0.678	0.898	0.961	0.957	0.930
Feat Morgan	0.447	0.289	0.979	0.902	0.906	0.940
	0.519	0.604	0.939	0.941	0.939	0.940
Atom Pair	0.459	0.411	0.959	0.922	0.922	0.940
Torsion	0.370	0.603	0.918	0.980	0.978	0.950
	0.364	0.573	0.939	0.960	0.958	0.950
Rdkit	0.671	0.666	0.878	0.941	0.935	0.910
Avalon	0.625	0.760	0.918	0.980	0.978	0.950
Layeres	0.742	0.545	0.959	0.941	0.940	0.950
	0.761	0.682	0.939	0.961	0.958	0.950

Conclusion

During this experimental work it was confirmed that different types of fingerprints capture different features of molecules. In addition, it was observed that the human judgement can be affected by the type of pharmacological group that belong the pair of active substances. In other words, certain molecules have specific chemical features, which are easy to perceive by the experts. Moreover, some fingerprints are able to capture chemical features present in the active substances of the same pharmacological group. The best models (those based on the BCI, Daylight, Unity, ECFP4, Extended, Standard, Morgan, Feat Morgan, Torsion, Avalon and Layers fingerprints) were able to reproduce over 95% of the human judgments. This success rate was increased to 98% using a simple data fusion approach in which a pair of molecules is classified as similar (or non-similar) when three or more of the individual fingerprints are in agreement. It was also noted that 1D descriptors do not correlate well with human judgement.

References

[a]Regulation (EC) No. 141/2000 of the European Parliament and Council of 16 December 1999.

[b] Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000 of the European Parliament and of the Council: review of the period of market exclusivity of medicinal products (2008/C 242/07) – 23 September 2009.

[c] Communication from the Commission on Regulation (EC) No 141/200 of the European Parliament and of the Council on orphan medicinal products – (2003/C 178/02) – 29 July 2003.

[d)] Regulation (EC) No. 847/2000 of the European Parliament and Council of 27 April 2000.

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