WHICH IS THE BEST FINGERPRINT FOR MEDICINAL CHEMISTRY?

Noel O'Boyle and Roger Sayle
NextMove Software, Cambridge, UK.

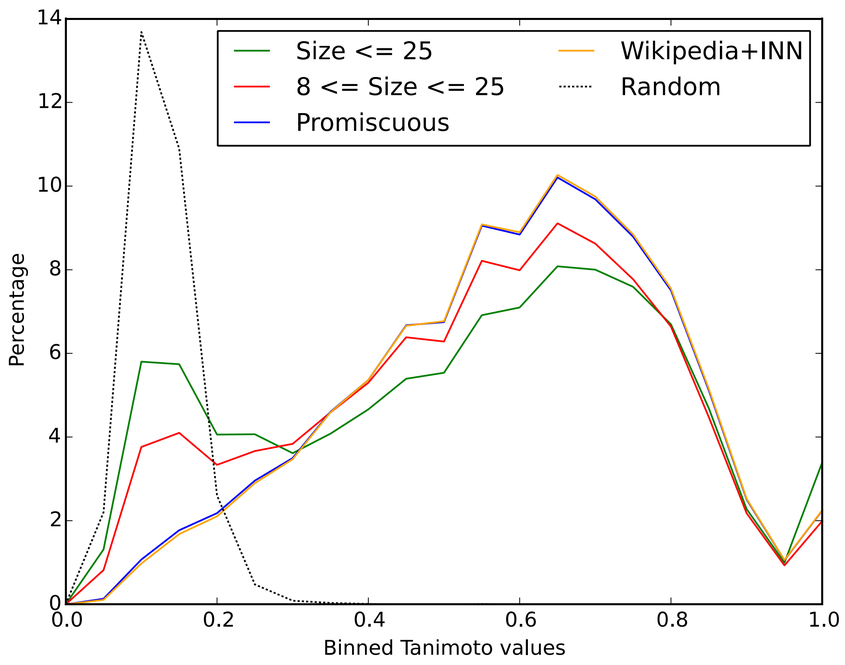
1. Introduction

Structural fingerprints are widely used in medicinal chemistry for similarity searching in virtual screens. While there are been several virtual screening studies aimed at determining the relative performance of fingerprints, these for the most part have been small-scale and lacking assessment of statistical significance. The exception is the study with which we compare our results, the benchmarking platform by Riniker and Landrum (*J. Cheminf.* **2014**, *5*, 26) which has 88 targets.

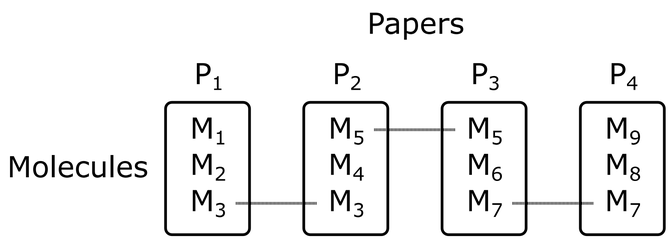
Here we describe a novel way of assessing the performance of structural fingerprints. We measure their ability to correctly rank order a series of molecules by structural similarity with respect to a reference.

2. A medicinal chemistry relevant definition of structural similarity

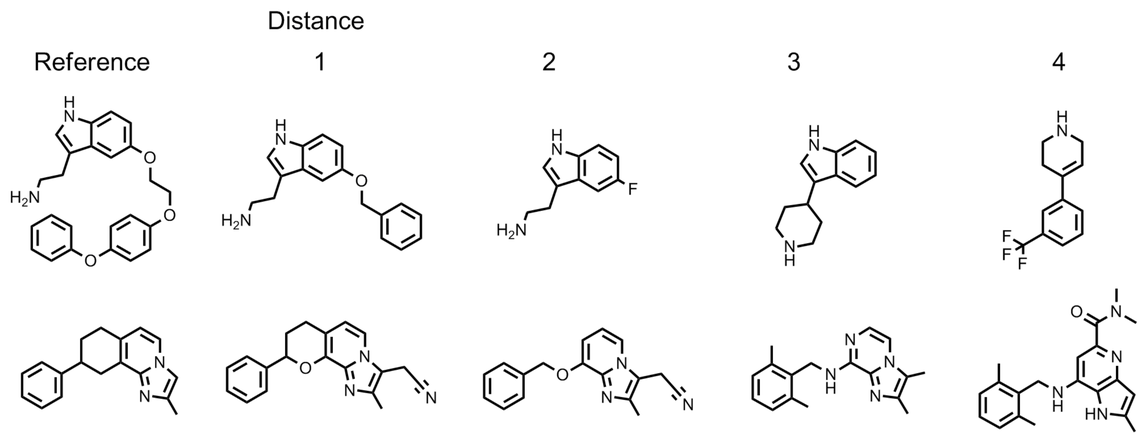
When are two molecules similar? For our purposes, we define molecules A and B as similar if a medicinal chemist would be likely to synthesise and test them around the same time as part of the same medicinal chemistry program. By this definition, molecules in the same assay in ChEMBL (i.e. in the same activity table in a paper) may be regarded as similar (with some caveats – e.g. the presence of known inhibitors). The image below shows the pairwise similarity of molecules in ChEMBL assays (according to ECFP4) and the effect of some simple filters to remove molecules likely to be dissimilar.



3. Multi-assay benchmark: Test ranking of structures from neighbouring papers

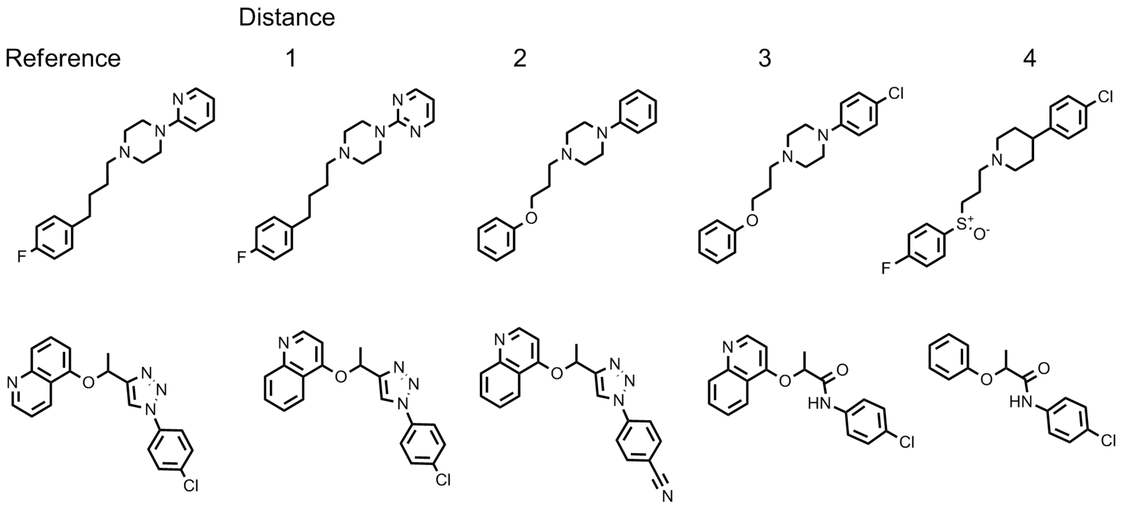


Given a reference molecule, a series of four molecules with decreasing similarity to the reference was generated by linking from one paper with activity data to another through molecules in common between both. The image above illustrates the concept: M1 and M3 are similar according to our definition, as are the pairs M3 and M5, M5 and M7, M7 and M9. We assume that relative to M1, structural similarity will decrease as one moves through the series M3, M5, M7, and M9. The final dataset contained 3629 such series.

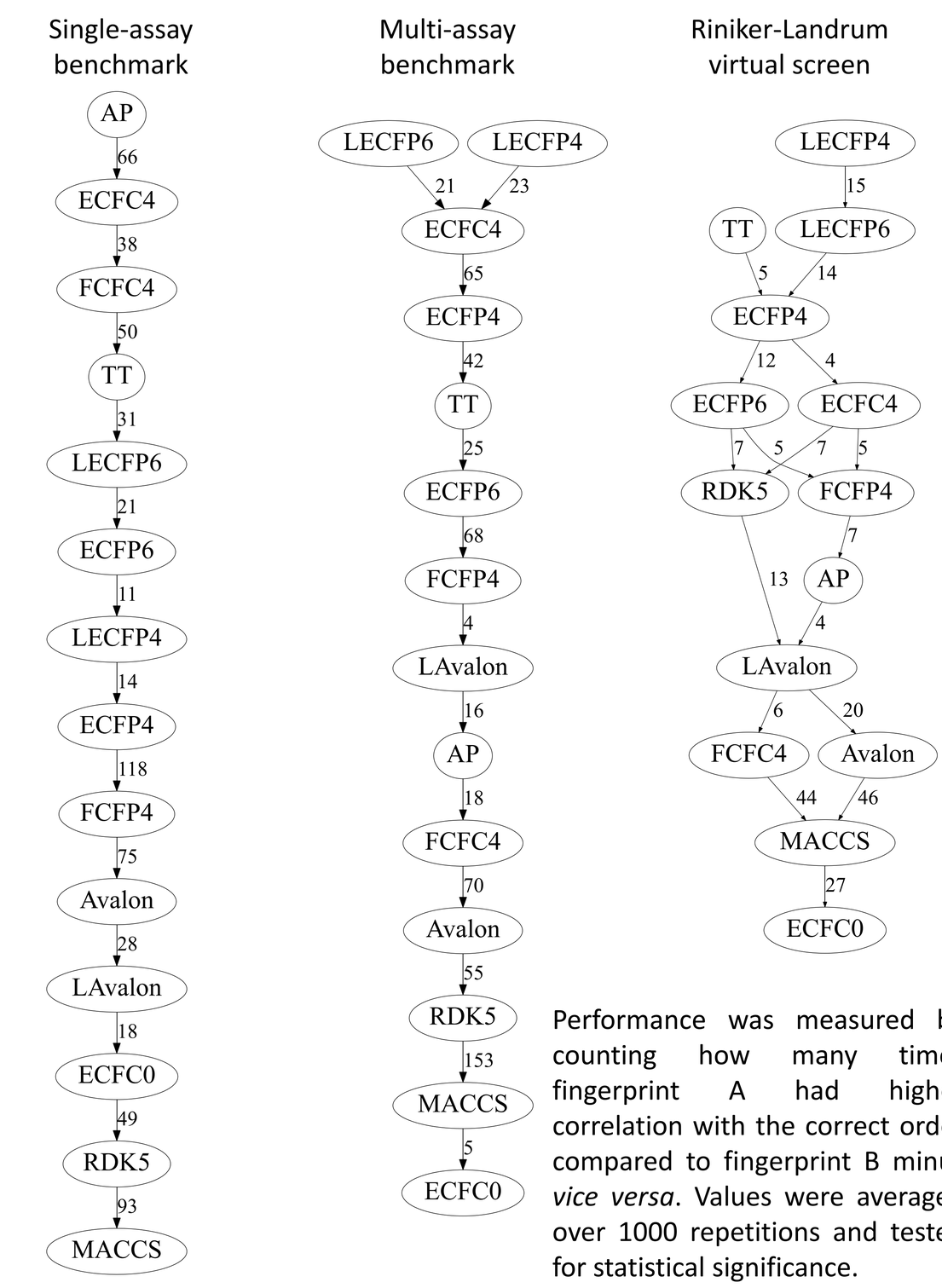


4. Single-assay benchmark: Test ranking of structures from the same paper

From the dataset of similar structures, we created a structural similarity benchmark of 4563 series each containing a reference molecule and four molecules in decreasing order of activity. Our assumption is that these molecules will tend to be arranged by decreasing structural similarity to the reference.



5. Benchmark results



Performance was measured by counting how many times fingerprint A had higher correlation with the correct order compared to fingerprint B minus *vice versa*. Values were averaged over 1000 repetitions and tested for statistical significance.

6. Conclusions

Here we provide conclusive evidence that extended-connectivity fingerprints of diameter 4 and 6 are among the best performing fingerprints when ranking diverse structures by similarity. The topological torsion fingerprint is also found to perform well at these tasks. When ranking very similar structures, the atom pair fingerprint outperforms the others tested; the count versions of the extended-connectivity fingerprints also perform well. Fingerprints to avoid include Daylight-type path-based fingerprints and MACCS keys.

NEXTMOVE SOFTWARE

www.nextmovesoftware.co.uk
www.nextmovesoftware.com

NextMove Software Limited
Innovation Centre (Unit 23)
Cambridge Science Park
Milton Road, Cambridge
UK CB4 0EY