Poster presentation

Assessing the selectivity of serine proteases inhibitors using structural similarity

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The selectivity of a pharmaceutical agent is crucial for its application as a drug. Several target families like protein kinases or serine proteases have a high intrafamiliar similarity that often leads to unwanted side effects in drug action. Therefore the estimation of the expected selectivity towards a specific target in early stages of the drug discovery pipeline has become an important research topic [1][2].

In most approaches to this problem either molecular descriptors or 3D-QSAR concepts have been used [1][2]. In this work we show that it is possible to encode the selectivity towards thrombin relative to the selectivities towards trypsin and factor Xa and to learn models of it by using machine learning techniques. To incorporate as much structural information as possible we transform molecular similarities into structured kernels [3] and use kernel-based machine learning techniques like support vector machines [4].

In contrast to other QSAR modeling approaches like partial least squares, the models learned by kernel methods can not be interpreted in a straightforward manner. To overcome this drawback we investigate the effects of the incorporation of different structural aspects beyond the plain topology (e. g. implicit atomic neighbourhood flexibility) and discuss possible interdependencies between them and the selectivity towards thrombin.

References

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