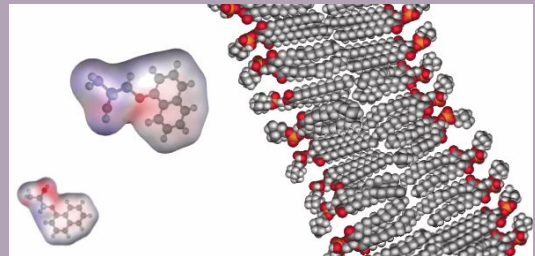


# Drug Permeability

It is becoming increasingly important to understand and predict the route of absorption of drug molecules so that new drug candidates can be designed with the correct physico-chemical profile. Human data on drug absorption is rare, however one notable exception to this is a study on human volunteers carried out at the *Uppsala Biomedical Centre* by *Winiwarter, et al.*, in 1998.

In this case study we show how multivariate data analysis using SIMCA-P software can identify desirable physicochemical properties for absorption and build a predictive model for new drug candidates. This work was originally published by Anders Karlén and co-workers at the Uppsala Biomedical Centre.



## Data

The effective permeability ( $P_{eff}$ ) of 22 drugs in human jejunum was measured in living patients. The 22 compounds selected for the study are transported across the intestinal membrane by different mechanisms. 15 compounds are transported by transcellular passive diffusion (PD), five use a carrier-mediated active transport mechanism (AT) and two are transported

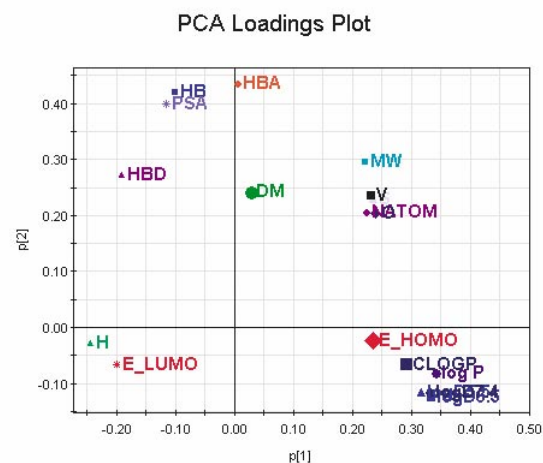
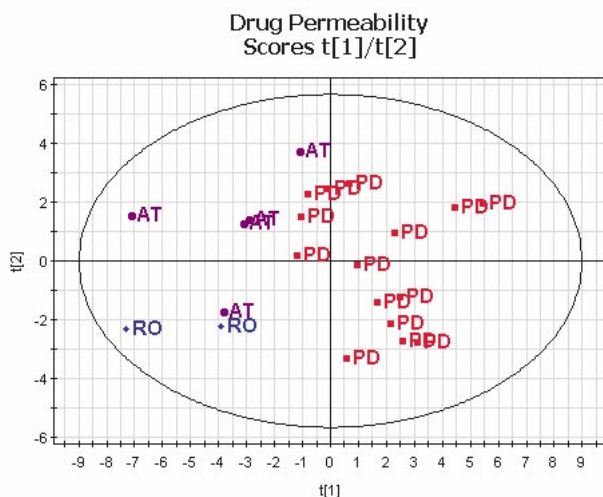
through a paracellular route (RO).

In order to characterise the properties of the 22 compounds multivariately, a set of 18 experimentally determined and theoretically derived molecular descriptors was compiled. The biological activity (BA) was the permeability,  $\log P_{eff}$ .

## Principal Components Analysis Overview

A PCA gave a 3-component model explaining 89% of the variation within the data. The first two components showed some discrimination of transport properties. To the right of the score plot (for observations) we find the 15 passively transported compounds and to the left the seven actively transported and paracellular transported compounds.

Looking at the corresponding directions in the loading plot (for variables), the passively diffused compounds are found to have high values of  $\log P$  and molecular weight. The actively transported drugs have high levels of hydrogen bonding (HBA, HBD, HB) and polar surface area (PSA). The paracellular compounds have low MW and high H and E-LUMO.



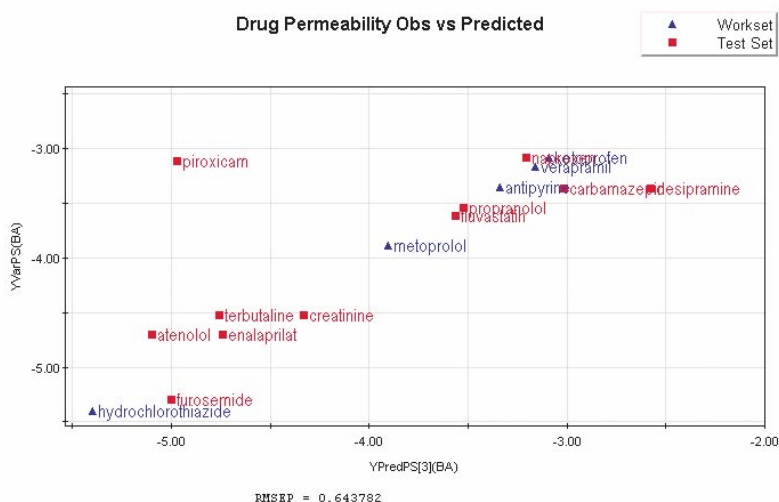
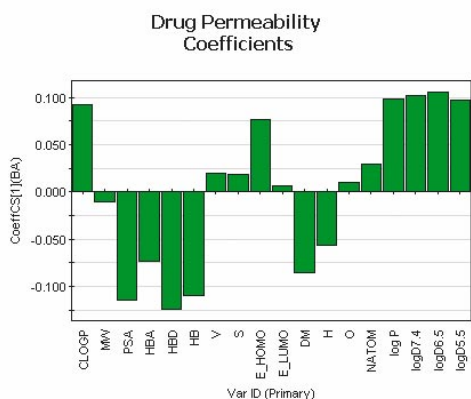
Plots from SIMCA-P 10.0 multivariate data analysis software.

## PLS Modelling of Absorption

A Partial Least Squares regression model (PLS) showed that the compound classes were too different to be included in the same QSAR model. A very good PLS model was however obtained for passively diffused compounds alone. The coefficient plot shows the sign and magnitude of the influence of the descriptors. Most of the descriptors are relevant to the QSAR model but the most important descriptors are very

simple, e.g., PSA and HBD. This makes it possible to obtain rough estimates of the biological response for previously untested drug candidates. Interestingly, the compound Piroxicam with known anomalous properties occurs as an outlier in the PLS prediction plot.

The amount of data is limited but the study gives a useful insight into the prediction of human drug absorption.



## Conclusions

- Principal Components Analysis can overview molecular property data and identify clusters and groupings.
- Comparison of the score and loading plots relates molecular properties to drug transport.
- Partial Least Squares regression (PLS) can be used to build models of drug absorption.

## Explanation of data set

Variables: CLOGP = calculated log P according to fragment constants; MW = molecular weight; PSA = polar surface area; HBA = hydrogen bond acceptors; HBD = hydrogen bond donors; HB = HBA + HBD; V = molecular volume; S = molecular surface area; E\_HOMO = energy of highest occupied molecular orbital; E\_LUMO = energy of lowest unoccupied molecular orbital; DM = dipole moment; H = hardness; O = ovality; NATOM = number of atoms; log P = octanol/water partition coefficient; log D7.4/6.4/5.5 = distribution coefficient in octanol/water at pH 7.4, 6.4, and 5.5; BA = log P<sub>eff</sub>. Observations: AT = Active Transport PD = Passive Diffusion RO = Paracellular Route

## References

S. Winiwarter, N.M. Bonham, F. Ax, A. Hallberg, H. Lennernäs and A. Karlén (1998) Correlation of Human Jejunal Permeability (in Vivo) of Drugs with Experimentally and Theoretically Derived Parameters—A Multivariate Data Analysis Approach, *Journal of Medicinal Chemistry*, 41, 4939-4949.

**SIMCA-P is our state-of-the-art “point and click” software for multivariate modelling and analysis. Huge data sets are quickly reduced to a few informative graphs.**



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