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The Block Relevance (BR) analysis to interpret chromatographic data: application to IAM chromatography in permeability studies

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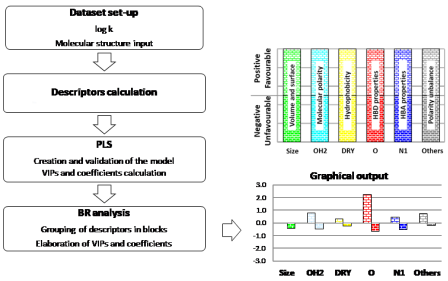
Statement of the Problem: The Block Relevance (BR) analysis is a computational tool that can be conveniently used to characterize and compare chromatographic scales. Immobilised Artificial Membranes (IAM) chromatography is expected to predict drug membrane permeability, a pivotal molecular property in drug discovery processes. The purpose of this study is to extract by BR analysis the balance of intermolecular interactions governing IAM descriptors (log K_w^{IAM},Δlog K_w^{IAM}) and verify their relationship with passive permeability. Methodology: Experimental: The RP-HPLC analyses were performed with 20 mM ammonium/acetate at pH 7.0 in water or in mixture with acetonitrile at various percentages. The stationary phase was IAM. PC.DD.2: its surface is formed by covalently bonding the membrane forming phospholipids to silica (Regis, 10cmx4.6cm 10um packing 300Å pore size). The flow rate was 1.0 ml/min. Computational: VolSurf+ (Vs+) software (version 1.0.7, http://www.moldiscovery.com) was used to generate PLS models with default settings and four probes (OH2, DRY, N1, and O probes that mimic, respectively, water, hydrophobic, HBA, and HBD properties of the environment). BR analysis was performed using an in-house software. Findings: BR analysis showed that successful prediction of permeability using log K_w^{IAM} alone is unlikely to occur but its combination with PSA can reasonably well predict PAMPA log P_{eff} of neutral and ionized compounds. Conversely, Δlog K_w^{IAM} is a polarity descriptor and thus plays a very relevant role in the prediction of cellular permeability Conclusion: IAM chromatography provides two descriptors (log K_w^{IAM} and Δlog K_w^{IAM}) of interest in the prediction of permeability, which is a crucial issue of any drug discovery project. Overall, this study highlights that, prior to their application to biological/toxicological topics, any chromatographic descriptor should be characterized for its information content using a tool like BR analysis.



Biography

Giulia Caron's primary scientific activity was lipophilicity, then she moved to the design, experimental determination and computational prediction of physicochemical properties related to ADME properties and to permeability measurements. The integration of Intramolecular Hydrogen Bonding (IMHB) considerations in drug design and the development and application of a tool named Block Relevance (BR) analysis to provide a mechanistic interpretation of QSAR/QSPR models based on the PLS algorithm are two of her main field of interest. To fit new drug discovery exigences she is now focusing on defining a set of experimental and in silico tools for molecular properties evaluation in the bRo5 chemical space.

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