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Do surface-based match solution-based techniques? The case of drug-liposome interaction

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ABSTRACT

The aim of the study is to check if the information about drug/liposome interactions provided by Surface Plasmon Resonance (SPR) is comparable with that provided by potentiometry in which liposomes are not immobilized on a solid support. To reach our aim we apply QSPR and BR analysis to data extracted from the literature and carefully inspected for their reliability. Results show that log K_D (SPR) is governed by a different balance of intermolecular interactions than log D_{lip} (potentiometry).

1. Introduction

Interactions of drugs and biological compounds with biomembranes are complex phenomena of paramount importance in both drug discovery and drug delivery. (van Balen et al., 2004; Pignatello et al., 2011). The understanding of drug membrane interaction is crucial both from a pharmacodynamic (PD) and a pharmacokinetic (PK) point of view. Firstly, drug membrane interactions govern drug binding with membrane-bound transporters, metabolizing enzymes and receptors, which have the binding sites located in the bilayer (Lukacova et al., 2013). Secondly, high and intermediate rates of trans-bilayer transport are responsible for good permeability properties, whereas too strong or too weak interactions lead to poor ADME profiles (Balaz, 2009).

Up to date a number of experimental methods have been proposed to investigate the affinity of drugs for biomembranes or artificial membranes models (e.g. liposomes): potentiometry, dialysis, ultracentrifugation, ultrafiltration, calorimetry, NMR and spectroscopic techniques, (van Balen et al., 2004; Lukacova et al., 2013), chromatography (Taillardat-Bertschinger et al., 2003), Surface Plasmon Resonance (SPR) (Abdiche and Myszka, 2004). An exhaustive review of all these methods is beyond the scope of this study.

According to Pignatello et al. (2011), three main kinds of lipid membrane models are reported in the literature: monolayers, vesicle forming bilayers (liposomes), and supported bilayers. Here we focus on liposomes. Notably, no computational method is available today to predict drug/liposome interaction. From an experimental point of view, the potentiometric technique (Avdeef et al., 1998) was shown to yield satisfactory estimates of lipophilicity in the liposome/water system by a few independent researchers (Escher, 2000; van Balen et al., 2004) and since it can be automated with modern titrators it is often preferred over the reference method, i.e. equilibrium dialysis.

SPR is emerging as an informative medium-throughput technology for hit validation (Patching, 2014) and thus a method to detect drug/liposome interactions based on this technology deserves particular attention. The conventional SPR technique requires one binding component to be immobilised on a sensor chip whilst the other binding component in solution is flowed over the sensor surface; a binding interaction is detected using an optical method that measures small changes in refractive index at the sensor surface (Patching, 2014). To measure drug/liposome interactions, liposomes are attached to a sensor surface, the drug is flowed over the sensor surface and the interactions between drugs and liposomes are monitored (Danelian et al., 2000). A few papers based on selected compounds demonstrate that when the SPR

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biosensor experiments are performed with care, the equilibrium, thermodynamic, and kinetic constants determined from this surface-based technique match those acquired in solution (Rich et al., 2001; Day et al., 2002; Swanenburg et al., 2005). However, this match is strongly dependent on the nature of the immobilized receptor and cannot be generalized.

To our knowledge, no relationship between drug/liposome interactions determined by SPR and liposome/water distribution coefficients is reported in the literature. SPR dissociation data were in fact only compared with lipid retention measurements obtained from parallel artificial membranes permeability assays (PAMPA) (Abdiche and Myszka, 2004).

To fill this gap, in this study we deconvolute the balance of the intermolecular forces governing a) the logarithm of the apparent binding affinities for drug interactions with liposome surfaces ($\log K_D$) and b) the logarithm of the liposomes/water distribution coefficients ($\log D_{lip}$).

To do that we apply a computational approach (named BR analysis) developed by us in 2012 (Ermondi and Caron, 2012). BR analysis allows the analysis of the balance of intermolecular interactions governing a given system using common 3D-QSAR/QSPR descriptors. These descriptors are aggregated into property-related groups (blocks), thus providing a convenient framework for comparison and interpretation of descriptors determined in different systems (Caron et al., 2013; Ermondi et al., 2014; Potter et al., 2014; Caron et al., 2015; Caron et al., 2016).

2. Materials and methods

2.1. The datasets

Experimental values of drug/liposomes interactions were taken from the literature as described below.

Dataset 1 refers to SPR data. The interaction with liposomes at pH 5.5 determined via SPR were expressed as the logarithm of the apparent binding affinities for drug interactions with liposome surfaces ($\log K_D$, see the original paper for details about K_D determination) (Abdiche and Myszka, 2004). K_D values were obtained from the histogram reported in Fig. 1 of the original paper and thus weak binders were not included in the study. The length of the bars was measured with a ruler and then converted in numerical values. The conversion was validated by comparing values cited in the original paper and values obtained by our conversion tool (for example tamoxifen: paper $K_D = 20$, our value $K_D = 20.14$; dibucaine: paper $K_D = 163$, our value $K_D = 163.35$). According to the definition, the lower K_D, the more bound the drug. The final dataset consists of 41 drugs. Dataset 1 includes 23 cations, 3 anions and 15 neutral drugs. The drug panel was analyzed against dioleoylphosphatidylcholine (DOPC) liposomes that were immobilized on Series S Sensor Chip L1.

Dataset 2 refers to the logarithm of the liposomes/water distribution coefficients ($\log D_{lip}$) at pH 7.0. Data were taken from four different papers which report $\log D_{lip}$ using a similar potentiometric equipment and method. Most compounds (14) were taken from the study by Balon et al., (1999). Rifabutin and paromomycin were discarded since potentiometry has some known limitations in the determination of log P of multiprotic substances and zwitterions. Seven compounds were extracted from Avdeef's paper (Avdeef et al., 1998). Lipophilicity data for four small organic molecules were taken from the study by Escher (2000) but nitro compounds were discarded since they need a peculiar computational treatment in VS+ which was beyond the scope of the study. Finally 8 drugs were extracted from the paper of Taillardat-Bertschinger et al. (2002). Dataset 2 includes 13 cations, 10 anions and 10 neutral drugs. All data refer to DOPC liposomes. Propranolol was reported in 3 out of 4 papers and all $\log D_{lip}$ values were very similar. When more than one value was present for the same compounds the Avdeef's value (Avdeef et al., 1998) was chosen.

If needed log D was calculated from $\log P^N$ and $\log P^I$ using the following equations

$$D = P^N \times \left(\frac{1}{1+10^{pKa-pH}}\right) + P^I \times \left(\frac{10^{pKa-pH}}{1+10^{pKa-pH}}\right) \text{ for bases}$$

$$D = P^N \times \left(\frac{1}{1+10^{pH-pKa}}\right) + P^I \times \left(\frac{10^{pH-pKa}}{1+10^{pH-pKa}}\right) \text{ for acids}$$

Since lipophilicity data were determined at pH 7.0 we verified that the ionization state of compounds did not significantly vary when passing from pH 5.5 to pH 7.0 (data not shown).

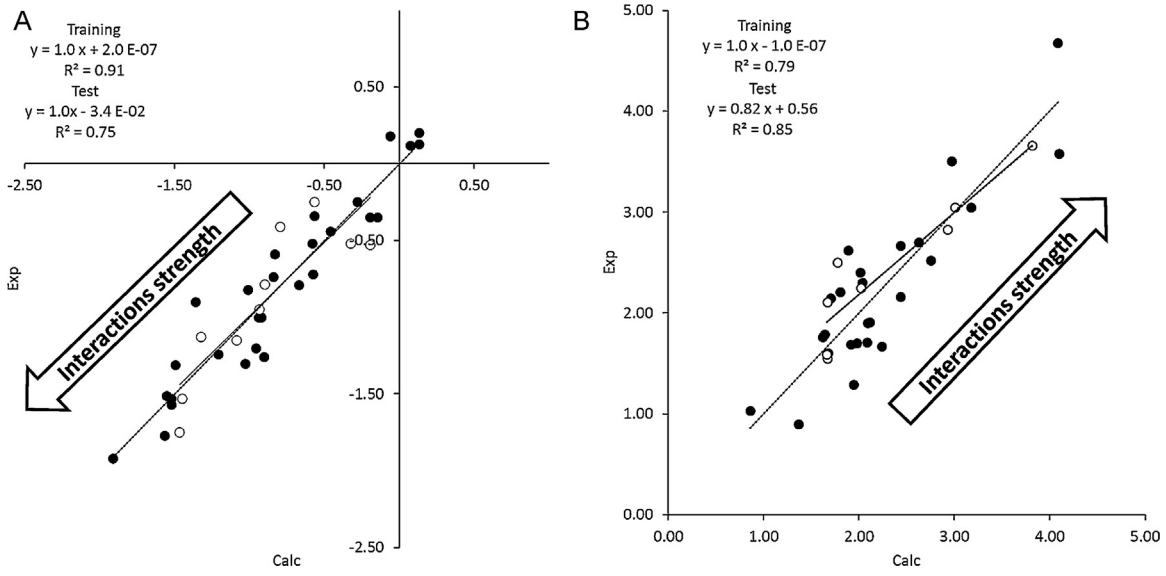

Fig. 1. Correlation between calculated and experimental values: A) log K_D and B) log D_{lip}.