

Exploring the Brainpeps database

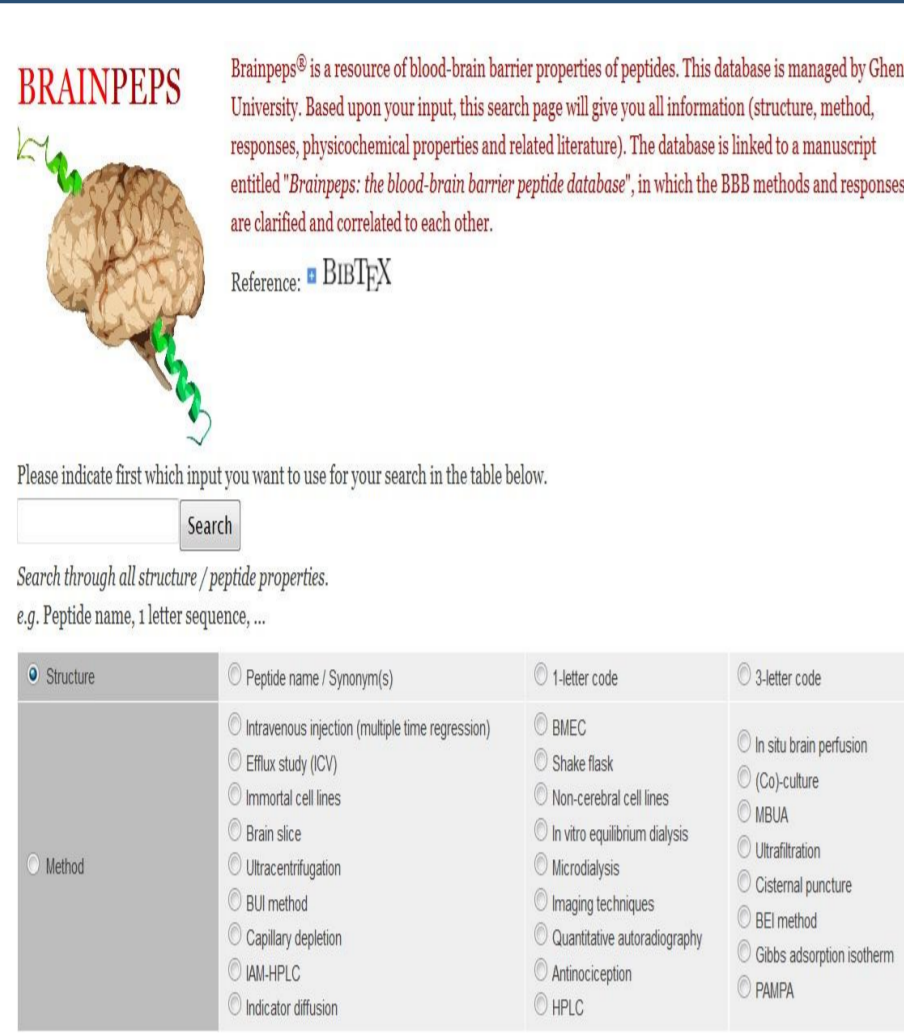
Sofie Stalmans, Matthias D'Hondt, Evelien Wynendaele, Nathalie Bracke and Bart De Spiegeleer*

Drug Quality and Registration (DruQuaR) group, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, B-9000 Ghent, Belgium.

*Corresponding author: bart.despiegeleer@ugent.be (O. Ref.: 2012-284d)

INTRODUCTION

Since the discovery that peptides can cross the blood-brain barrier (BBB), doors have been opened to new therapeutics for Central Nervous System (CNS) diseases and pain management. Recently, we have constructed the Brainpeps database (<http://brainpeps.ugent.be>) to give an overview of the currently available BBB-transport data of peptides, which are scattered in the literature [1]. One possible application of the database is the study of structure-property relationships (QSPRs).



OBJECTIVES

- Exploration of the Brainpeps database, focussing on the BBB-influx data.
- Making the variety of BBB-influx responses comparable by defining an unified response.
- Constructing a predictive model for BBB-behaviour of peptides and their impurities, using the unified response as well as chemo-molecular and experimental descriptors.

RESULTS

1. DATA EXPLORATION OF RESPONSES

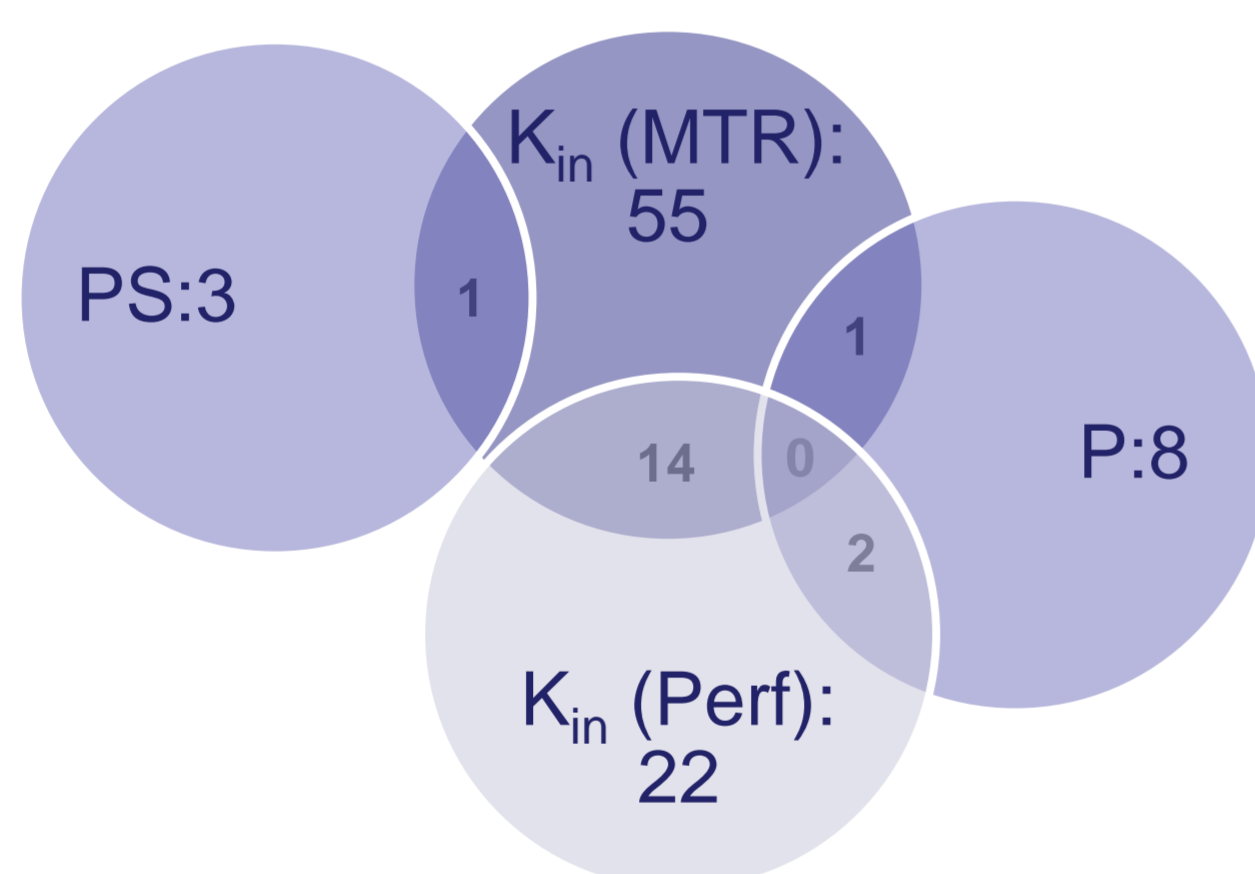


Fig 1. Statistics of BBB-influx data in Brainpeps database (numbers are indicated).

- 135 peptides in database: 68 peptides with BBB-influx data.
- BBB-influx responses: K_{in} (Multiple Time Regression (MTR) and *in-situ* brain perfusion (Perf)), Permeability coefficient/constant (P) and Permeability-Surface area coefficient (PS).
- No statistical correlation between different BBB-influx responses.

2. IN-SILICO DESCRIPTORS AS MODEL FACTORS

- 3D-optimized structures of a set of 51 peptides were used to calculate ± 3250 chemo-molecular descriptors, which were corrected for constants and autoscaled using the z-score \Rightarrow 2 datasets:
 - All chemo-molecular descriptors (281).
 - Selected descriptors, based upon peptide interactions at the BBB (39):

Property	Typical descriptors
Hydrophobicity	logP, logSumAA (RP-RT descriptor [2]), aromaticity (e.g. ARR, nCIC)
Hydrogen bonding	nHDon, nHAcc
Topological	Polar Surface Area (PSA), Jhetv
Constitutional	Molecular Weight (MW), mean atomic van der Waals volume (Mv), number of rotatable bonds (RBN)
Charge	pI, charge at pH = 7.4

- Descriptors, correlated with MW, were normalized by dividing by the MW.

3. EXPERIMENTAL DESCRIPTORS

- Retention mechanisms of peptides in HPLC systems ~ interactions at BBB \Rightarrow Determination of retention volumes in 16 chromatographic systems [2]:
 - 4 different Halo® HPLC columns \times 4 different mobile phases

4. TOWARDS AN UNIFIED RESPONSE

- Classification based upon Box-Whisker distribution of each BBB-influx response in the database, resulted in 5 classes (Fig 2).

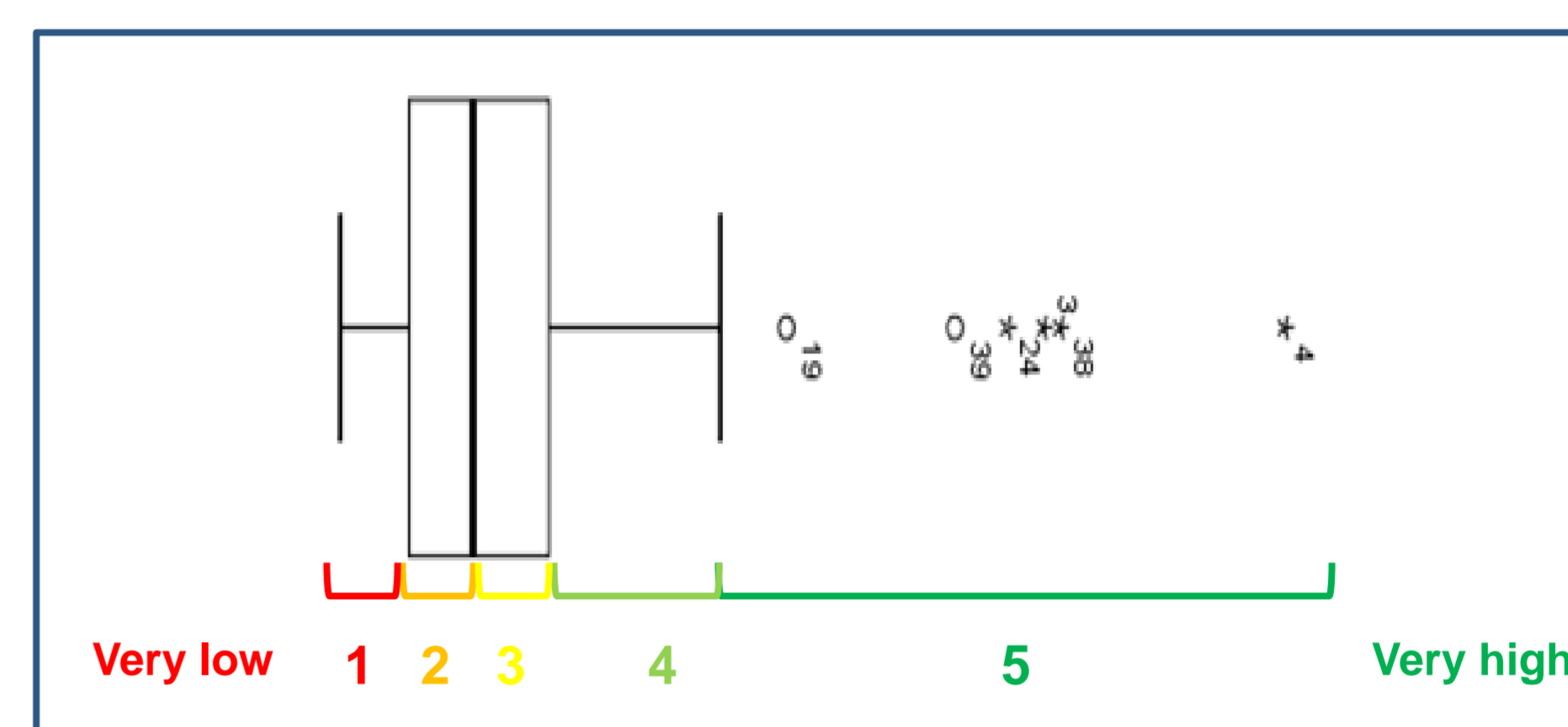


Fig 2. Box-Whisker distribution of K_{in} (MTR) responses for influx.

- Conversion of classes to percentage influx value (Fig 3).

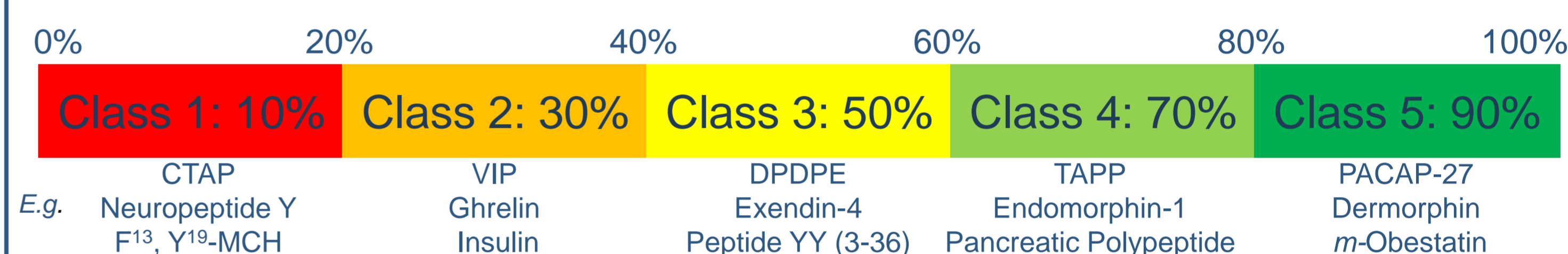


Fig 3. Conversion of classes to percentage values supplemented with class representatives.

- If peptide is classified in > 1 class \Rightarrow mean of percentage influx is calculated.
- Verification of classification by comparison of the influx class with the estimation of BBB-influx by the authors of the corresponding article (Fig 4).

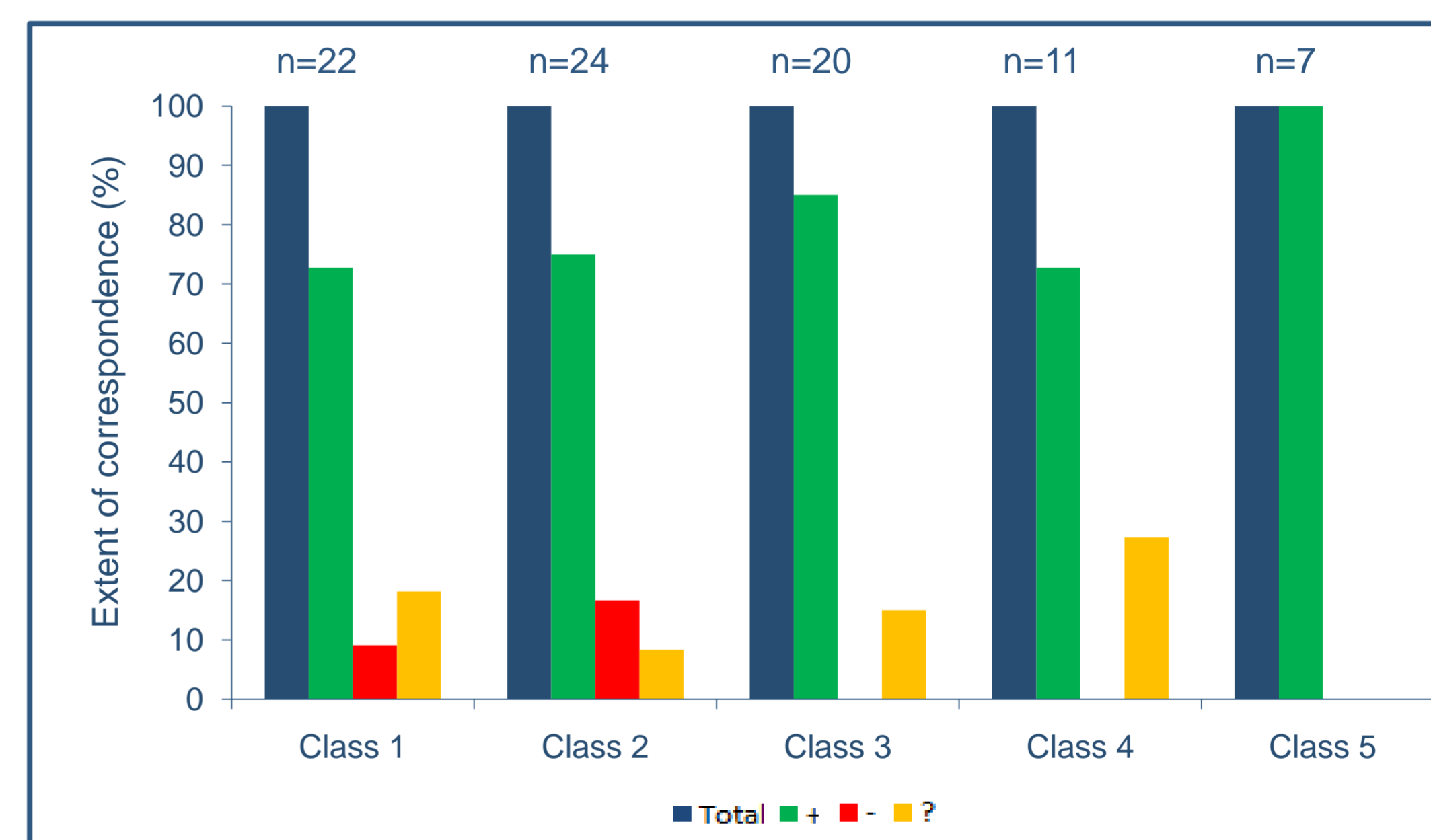


Fig 4. Verification of classification of peptides by comments authors.

\Rightarrow $\pm 80\%$ correspondence in classification.

5. MODELLING: BBB-INFLUX UNIFIED RESPONSE = f(DESCRIPTORS)

Multiple Linear Regression (MLR; Entry: 0.1 and Removal: 0.5)

5.1 In-silico descriptors

Dataset 2: % influx = $-2.4 + 2.4 \text{ nHDon/MW} - 0.23 \text{ pI}$.

$\Rightarrow R^2 = 0.131$: only $\pm 15\%$ of variability is explained.

5.2 Experimental chromatographic descriptors

% influx = $2.4 \cdot 10^{-5} + 1.4 \text{ RV (Phen-Hex/FA-ACN)} - 1.2 \text{ RV (C18/FA-ACN)}$.

$\Rightarrow R^2 = 0.268$: only $\pm 25\%$ of variability is explained by the model.

CONCLUSIONS

By exploring the Brainpeps database, we developed an unified response for BBB-influx of peptides, which permits to compare the BBB-influx of peptides in an one-merit figure. Using this classification, predictive MLR models for BBB-influx were constructed, using experimental and chemo-molecular descriptors. These MLR models explain only 20-25% of the variability.

REFERENCES

- Van Dorpe et al. Brainpeps: the blood-brain barrier peptide database. Brain Structure and Function (2012), 217, 687-718.
- D'Hondt et al. Reversed-phase fused-core HPLC modelling of peptides. Journal of Pharmaceutical Analysis (2012), Accepted for publication.