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Can BDDCS class be used to explain differences in the prediction of human oral bioavailability from animal data using a threshold-based model?

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Background

- It has been shown that animal oral bioavailability cannot quantitatively predict human oral bioavailability[1].
- Receiver Operating Characteristic (ROC) analysis of the dataset in [1] suggested that animal bioavailability data can be employed for the qualitative prediction of human oral bioavailability, that is high or low.

Purpose

- A threshold-based model has been developed to predict high/low human oral bioavailability (F_{Human}) from animal oral bioavailability (F_{Animal}).
- Herein, the results obtained with this model are analysed according to Biopharmaceutics Drug Disposition Classification System (BDDCS) Class

Methods

- The oral bioavailability of 182 compounds in humans and preclinical species - rat, dog, non-human primates (NHP) - were collated from the literature [1].
- A model for prediction of high (≥ 50%, positive) and low (< 50%, negative) F_{human} from high/low F_{animal} was constructed by selecting the most predictive thresholds for high/low F_{animal} (rat 22%, dog 58%, NHP 35%).
- The compounds were then assigned to a BDDCS Class either according to the lists provided by Benet et al. [2] or based upon other literature data.
- Class distribution was then compared within each of the threshold-based outcome group (i.e. true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN)).
- Significance of the difference between the initial BDDCS class distribution and the BDDCS class distribution of the compounds separated by the outcomes of the threshold-based model were tested by the Fisher's Exact Test for proportions.

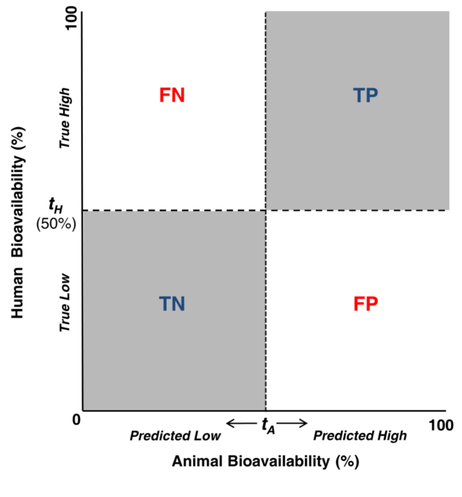

Figure 1. Threshold based predictions of human oral bioavailability from animal data.
FN, False negatives; **TP**, True positives; **TN**, True negatives; **FP**, False positive; t_A, Animal high/low bioavailability threshold; t_H, human high/low bioavailability threshold.

Conclusion

- An outcome analysis of a threshold-based model for the prediction of F_{human} from F_{animal} according to BDDCS class was performed.
- Sub-categorization of the compounds according to BDDCS class did not show any significant trends with respect to threshold-model class (TP, TN, FP, and FN).
- Therefore, for the current dataset, BDDCS class cannot explain differences in prediction of F_{human} from F_{animal} obtained using the threshold-based model.

Acknowledgements

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References

1. Musther, H., et al. Eur. J Pharm. Sci. (2013). DOI: 10.1016/j.ejps.2013.08.018
2. Benet. L.Z., et al. AAPS J. 2011, 13(4), 519-47.
3. Broccatelli, F., et al. Mol. Pharm. 2012, 9(3), 570-580.
4. Benet. L.Z. J. Pharm. Sci. 2013, 102(1), 34-42.

Results

- The majority of the drugs investigated were BDDCS Class 1 (47%), followed by Classes 3 (25%), 2 (22%) and 4 (6%), consistent with the BDDCS distribution for marketed drugs [3, 4]. (**Figure 1**)

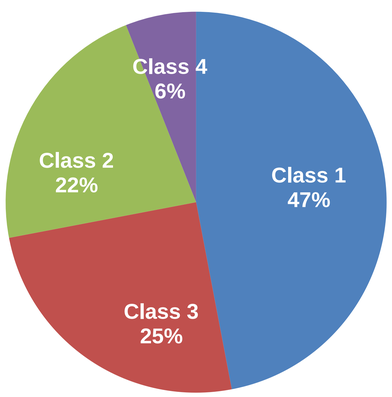

Figure 1: BDDCS class distribution for the compounds employed for the analysis.

- **Tables 1 to 3** show the results for the BDDCS class distribution for the compounds analysed and the number of compounds that were separated according to the thresholds-based model for the qualitative prediction of human oral bioavailability.

Table 1. Number of compound s by BDDCS class and threshold-based model outcome
(Rat data)

BDDCS	n	TP	FN	TN	FP
Class 1	61	22	9	25	5
Class 2	25	8	6	9	2
Class 3	30	16	3	8	3
Class 4	9	4	3	1	1
Total	125	50	21	43	11

Table 2. Number of compounds by BDDCS class and threshold-based model outcome
(Dog data)

BDDCS	n	TP	FN	TN	FP
Class 1	59	21	9	16	13
Class 2	24	13	1	4	6
Class 3	30	15	4	9	2
Class 4	9	5	2	2	0
Total	122	54	16	31	21

Table 3. Number of compound s by BDDCS class and threshold-based model outcome
(NHP data)

BDDCS	n	TP	FN	TN	FP
Class 1	17	6	0	11	0
Class 2	8	5	1	2	0
Class 3	13	9	2	2	0
Class 4	3	1	1	1	0
Total	41	21	4	16	0

There was no significant difference between the overall BDDCS class distribution and the distribution within each threshold-model class (TP, TN, FP and FN) for any of the preclinical species ($p > 0.1$). (**Figure 2**)

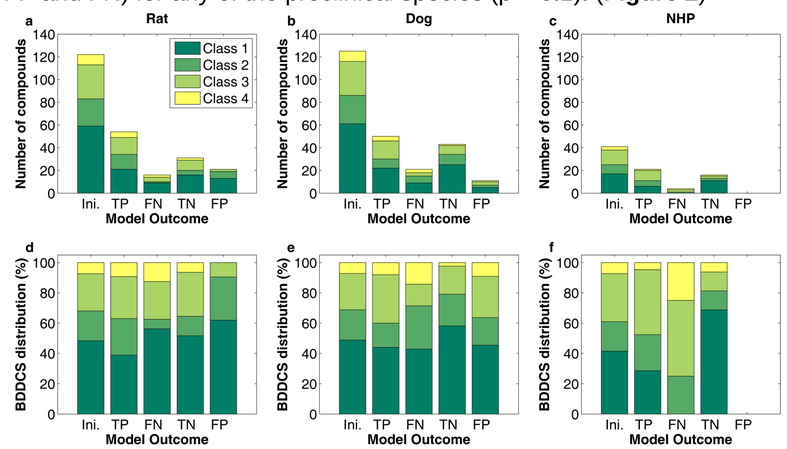

Figure 2. Number of compounds and BDDCS class distribution for rat(**a**), dog(**b**) and NHP(**c**) as function of the outcome of the threshold-based model. Distribution all the compounds analysed and separated by outcome of the threshold-based model (in percentages of the number of compounds) for rat(**d**), dog(**e**) and NHP(**f**), respectively.
Ini: Total number of compounds analysed and its BDDCS class distribution.