Qualitative model for the prediction of high/low human oral bioavailability from animal bioavailability data employing ROC analysis

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Background

- Oral bioavailability is considered a key parameter during drug development. However, it is often unknown during early -mid stages of the drug development process.
- It is a common practice to employ animal models for the *in vivo* determination of oral bioavailability in order to estimate human oral bioavailability of a new drug candidate.
- However there is a poor correlation between animal and human bioavailability[1].

Aims and objectives

- To develop a Receiver Operating Characteristic (ROC) analysis to evaluate the performance of animal oral bioavailability (F_{animal}) data for the qualitative prediction of human oral bioavailability (F_{human}).
- To identify the optimal cut off values of high/low F_{animal} for the qualitative prediction of F_{human} from F_{animal} data.

Materials and methods

- Oral bioavailability data for both human and preclinical species (mouse, rat, dog and non-human primates (NHP)) for 184 compounds were collated from literature as described elsewhere [1].
- For implementation of the ROC analysis, F_{human} was defined as high (≥ 50%) or low (< 50) as shown in **Figure 1**.
- The construction of the ROC curves was implemented in Matlab 2012a by varying the animal threshold (t_A) for high and low F_{animal}, the resulting error rates (**Table 1**) for each t_A were recorded, and plotted.
- Animal models for the prediction of high and low F_{human} were evaluated by the area under the ROC curve (AUC)[2-3].
- Optimal cut off values for the F_{animal} were calculated by intercepting a line of slope ***S*** (**Eq. 1**) to the resulting ROC curves[2].

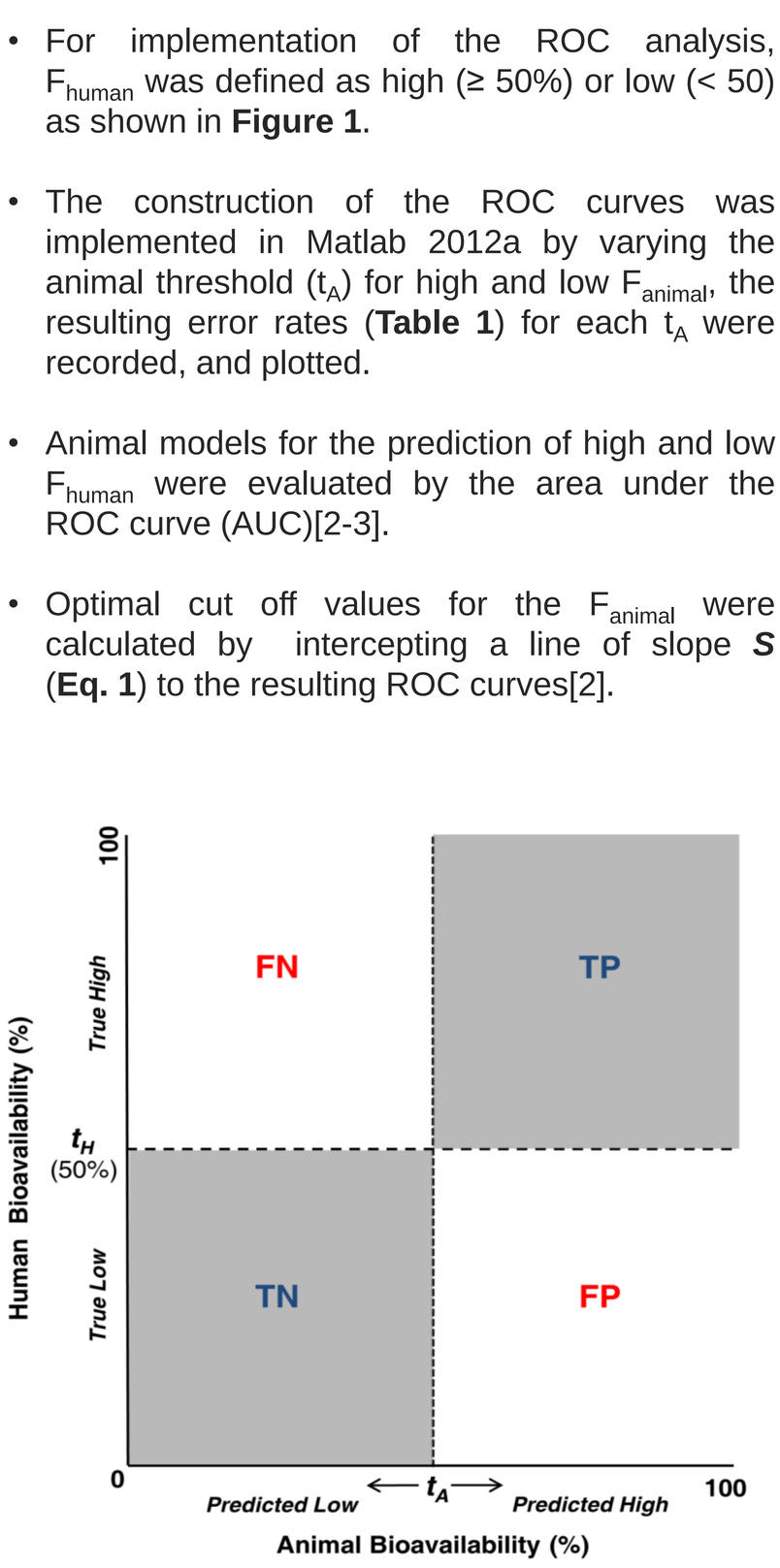

Figure 1. Threshold based predictions of human oral bioavailability from animal data. FN, False negatives; TP, True positives; TN, True negatives; FP, False positive; t_A, Animal high/low bioavailability threshold; t_H, human high/low bioavailability threshold.

Materials and methods (cont'd)

Table 1. Definition and formulae for the evaluation of the binary classification system

Parameter	Formula	Probability
Sensitivity (TPR)	$\frac{TP}{TP+FN}$	P[high F_{animal}| high F_{human}]
Specificity (TNR)	$\frac{TN}{TN+FP}$	P[low F_{animal}| low F_{human}]
PPV	$\frac{TP}{TP+FP}$	P[high F_{human} | high F_{animal}]
NPV	$\frac{TN}{TN+FN}$	P[low F_{human} | low F_{animal}]
FPR	$1-TNR$	P[high F_{animal}| low F_{human}]

TPR, true positive rate; TNR, true negative rate; PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate.

$$S = \frac{cost(FP) - cost(TN)}{cost(FN) - cost(TP)} \times \frac{N}{P} \qquad \textbf{Eq. 1}$$

Where:

- **cost(FP)** and **cost(FN)** : hypothetical cost of false positives and negatives (set up to 1).
- **cost(TP)** and **cost(TN)**: hypothetical cost of true positives and negatives (set up to 0).
- **N** and **P**: number of high and low F_{human} values.

Results

- The results from the ROC curve generation are summarized in **Table 2**.
- When F_{animal} was considered for all species combined, the resulting ROC curve AUC was 0.79 (**Figure 2**). Species specific AUC values were 0.82, 0.73, 0.80 and 0.96 for mouse, rat, dog and NHP, respectively (**Figure 3**).
- All of the preclinical species showed significant improvement in the predictions of F_{human} as compared to a random classification (AUC = 0.5).
- Optimal cut off values for F_{animal} and the corresponding error rates are summarized in **Table 3**.

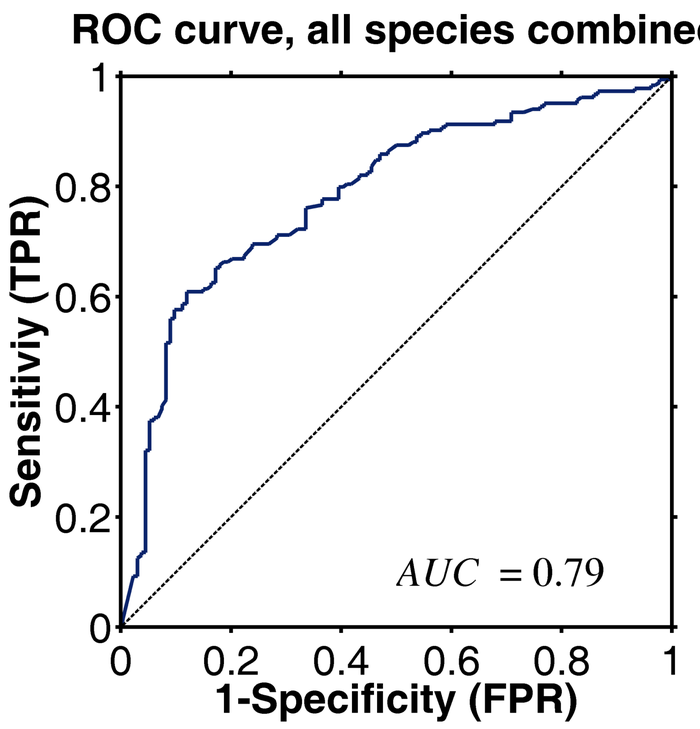

Figure 2. ROC curve for the human versus animal bioavailability dataset for all the preclinical species (mouse, rat, dog and NHP) combined. The dashed line corresponds to the line for random classification, AUC =0.79 for the overall dataset.

Table 2. Area under the ROC curve for all the preclinical species

Species	All	Mouse	Rat	Dog	NHP
n	318	30	122	125	41
ROC AUC	0.79	0.82	0.73	0.80	0.96
(95% CI)[a]	(0.73, 0.83)	(0.61, 0.94)	(0.63, 0.82)	(0.70, 0.87)	(0.87, 0.99)

Notes: 'n' is the number of data points; all AUC values were significantly different than 0.5 (p <0.005); 95% CI was determined by bootstrap (N = 10000)

Results (cont'd)

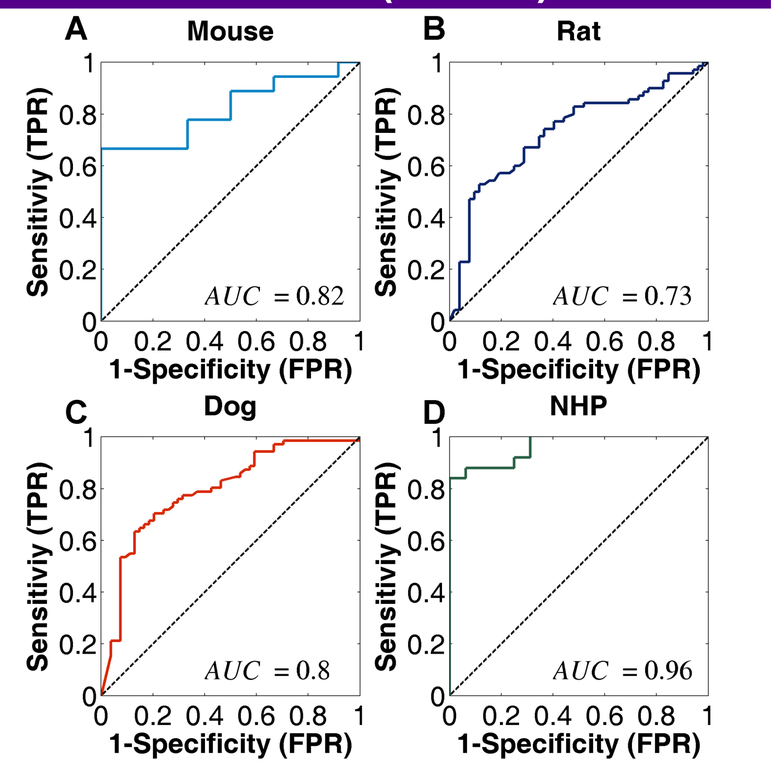

Figure 3. ROC curves for the human versus animal bioavailability dataset by preclinical species. Dashed line corresponds to the line for random classification:

A. Mouse ROC curve, AUC = 0.82
B. Rat ROC curve, AUC = 0.73
C. Dog ROC curve, AUC = 0.80
D. NHP ROC curve, AUC = 0.94

Table 3. Optimal cut off values for F_{animal} derived from cost analysis

Species	Opt. t_A (%)	Specificity	Sensitivity	NPV	PPV
All	47	0.82	0.66	0.64	0.84
Mouse	67	1.00	0.67	0.67	1.00
Rat	22	0.60	0.77	0.66	0.72
Dog	58	0.80	0.70	0.67	0.82
NHP	35	1.00	0.84	0.80	1.00

Opt. t_A ,Optimal cut off values for $F_{animal.}$

Discussion and conclusions

- The results suggest that a value around 50% for F_{animal} can predict high and low F_{human} with a high sensitivity and specificity.
- Species specific results suggest a similar approach, where NHP shown to be the best prediction. The latter is consistent with the values reported previously for point-wise correlations [1]. In addition the cut off values are consistent with previous values reported for rat [4,5].
- The resulting cut off values can be employed to make "go/no-go" decisions during the development of new drug candidates.

Acknowledgements

A.O-M. is funded by a PhD scholarship awarded by CONICYT Chile and a President's Doctoral Scholar Award of The University of Manchester.

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