QSAR Modeling of Caco-2 Permeability for the Estimation of Oral Bioavailability

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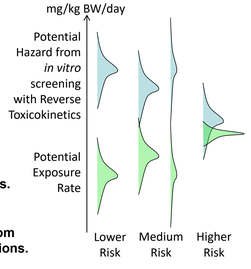
Background

- Data from high throughput *in vitro* screening assays describe potential **hazard**.
- **Toxicokinetics** may be used to determine corresponding oral equivalent doses for comparison to potential **exposure** rate (Wetmore *et al.* 2015).
- The extrapolation of *in vitro* hazard to *in vivo* oral equivalent doses may be improved by accurate definition of the **fraction absorbed (F_{abs})** through the intestine.
- F_{abs} are not frequently available for non-pharmaceuticals.
- The **Caco-2** assay allows for measurement of an apparent **permeability rate (P_{AB})** that is highly correlated with F_{abs} (Artursson *et al.* 2001).
- F_{abs} , combined with **gut metabolism (F_g)** and first pass hepatic clearance (F_{fp}) are used to estimate the **oral bioavailability (F_{bio})**.



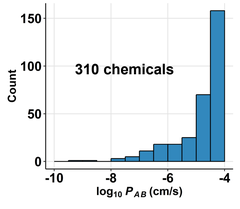
In this work, the Caco-2 permeability rate was measured for 310 ToxCast chemicals. Measured values and QSAR predicted results were used for the estimation of oral bioavailability (F_{bio}).

Potential improvements in toxicokinetics using more accurate estimates of F_{bio} from Caco-2 data may enable the use of *in vitro* toxicity data to inform regulatory decisions.

Caco-2 Permeability

Measured Permeability

- **Caco-2 cells**, developed from human colon carcinoma cells, form a polarized monolayer that behaves similarly to the human intestinal epithelium.
- Permeability was measured from apical to basolateral (P_{AB}) and basolateral to apical (P_{BA})
- Majority of chemicals (71%) have high P_{AB} (>1x10^{-5} cm/s), similar to that of the high permeability control (warfarin)
- Most chemicals (88%) had efflux ratio (P_{BA} /P_{AB}) < 2

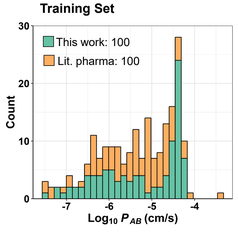


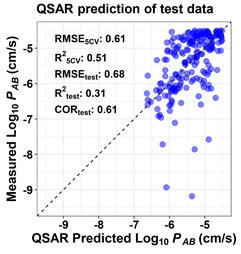
Random Forest QSAR for P_{AB}

1. Training set of values from our Caco-2 data and literature (ChEMBL, Ohagan *et al.*) pharmaceutical data
2. Use PaDel descriptors
3. Drop features with near zero variance
4. Recursive feature elimination, 5 fold cross-validation
5. Tune number of variables tried at each branch (mtry), 5 fold CV

QSAR Model Results

- Results for test set (P_{AB} measured in this work) slightly worse than estimates from 5 fold-CV
- Possibly need more environmental chemical data to achieve improved result





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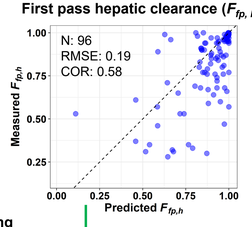
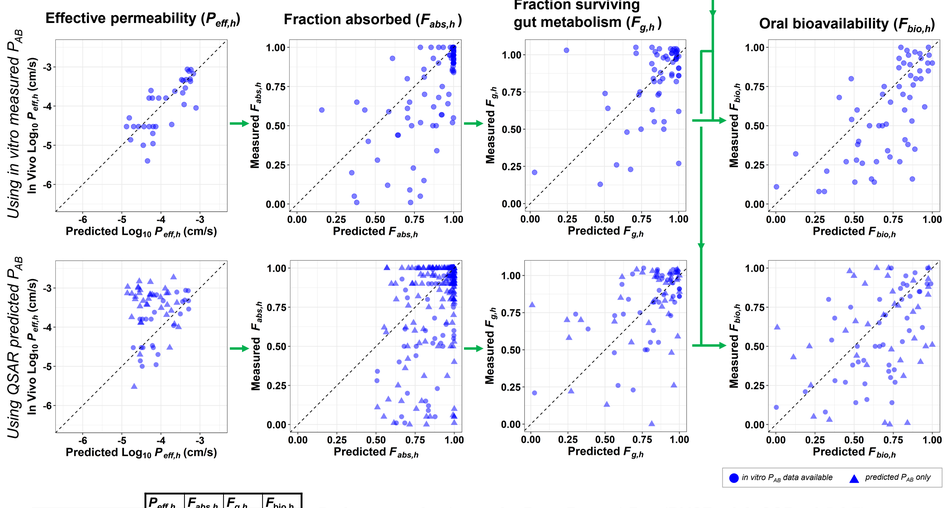
Predicting Human Oral Bioavailability

Do measured P_{AB} provide reasonable estimates of F_{bio}?

How do estimates using QSAR predicted P_{AB} compare?

- Determine $F_{bio,h}$ based on 1) *in vitro* measured P_{AB} (using our values and literature) and 2) QSAR model predicted P_{AB} for chemicals outside of the training set.
- Use literature models incorporating P_{AB} and *in vitro* measurement for intrinsic hepatic clearance (Cl_{int}) and fraction of unbound chemical in plasma (f_{up}).
  - Effective permeability (P_{eff}) – empirical model, Darwich *et al.* 2010
  - Fraction absorbed (F_{abs}) – empiricical model, Darwich *et al.* 2010
  - Fraction surviving gut metabolism (F_g) – Q_{gut} model, Yang *et al.* 2007
  - Fraction surviving first pass hepatic clearance (F_{fp}) – based on f_{up} and Cl_{int}
  - $F_{bio} = F_{abs}\, F_g\, F_{fp}$
- Compare results to literature *in vivo* measured data (Dahlgren et al. 2015, Varma and Obach *et al.* 2010, Paixao *et al.* 2012) for pharma chemicals outside the training set.





		$P_{eff,h}$	$F_{abs,h}$	$F_{g,h}$	$F_{bio,h}$
Using *in vitro* P_{AB}	N	33	109	58	58
	RMSE	0.42	0.22	0.22	0.25
	COR	0.77	0.71	0.50	0.66
Using QSAR P_{AB}	N	63	286	83	83
	RMSE	0.89	0.27	0.25	0.30
	COR	0.17	0.48	0.46	0.43

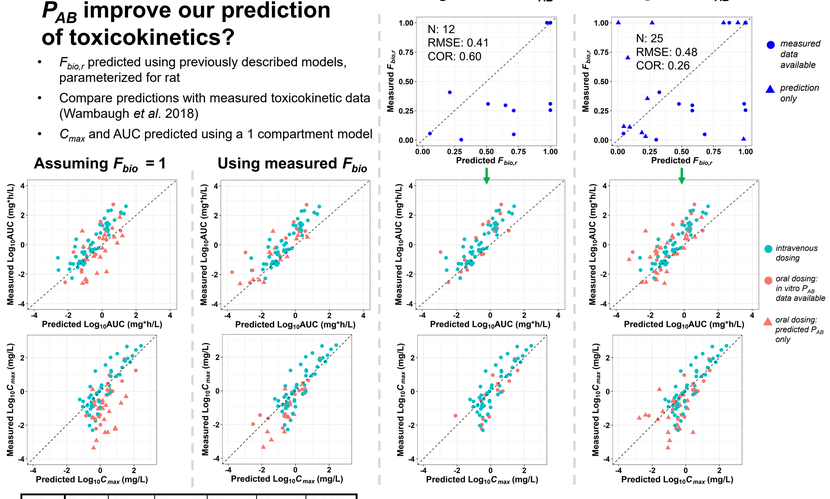
Performance of estimates for $F_{abs,h}$, $F_{g,h}$, and $F_{bio,h}$ (RMSE ~ 0.2, COR ~ 0.5-0.7) incorporating measured P_{AB} comparable to estimates of $F_{fp,h}$ based on *in vitro* measured f_{up} and Cl_{int} (RMSE ~ 0.2, COR ~ 0.6).

Results for $F_{bio,h}$ based on QSAR P_{AB} perform only slightly worse (RMSE ~ 0.3, COR ~ 0.4), better performing model may be achievable.

Toxicokinetics in Rat with F_{bio} Estimates

Do F_{bio} estimates based on P_{AB} improve our prediction of toxicokinetics?

- $F_{bio,r}$ predicted using previously described models, parameterized for rat
- Compare predictions with measured toxicokinetic data (Wambaugh *et al.* 2018)
- C_{max} and AUC predicted using a 1 compartment model



Value	Route	Stat.	F_{bio} = 1	Meas. F_{bio}	Meas. P_{AB}	QSAR P_{AB}
AUC	All	RMSE	0.96	0.98	0.99	1.05
		COR	0.75	0.86	0.86	0.79
C_{max}	All	RMSE	1.14	0.76	0.76	0.90
		COR	0.66	0.86	0.83	0.76

Collectively, **improved correlation of intravenous and oral dosing predictions with measured data** when using estimated F_{bio} (using QSAR predicted P_{AB} or measured P_{AB}) for oral dosing predictions relative to F_{bio} = 1 for this limited set of chemicals

Summary

- P_{AB} was measured for 310 ToxCast chemicals; 80 % have estimated $F_{abs,h}$ ~ *1*
- Estimates for $F_{bio,h}$ incorporating either Caco-2 measured P_{AB} or QSAR predicted P_{AB} seem reasonable for high throughput applications
- Correlation of measured oral and i.v. dosing kinetics with predicted results was improved when oral dosing estimates incorporate predicted $F_{bio,r}$
- Future work may evaluate models using collection of literature pharmacokinetic studies with oral dosing

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