Rapid Prototyping of Physiologically-Based Toxicokinetic (PBTK) Models

3504/P479

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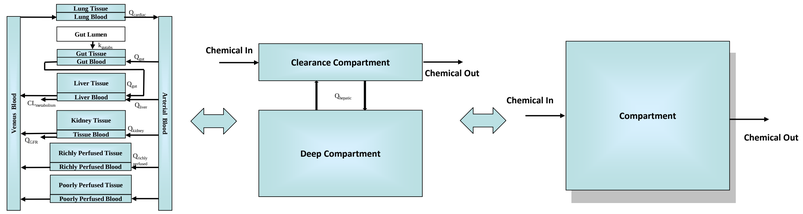
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Introduction

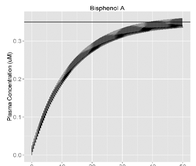
- Rapidly parameterized generic PBTK models allow *in vitro* to *in vivo* extrapolation (IVIVE) for chemicals tested for bioactivity via high-throughput screening and enable exposure inferences from blood/serum biomonitoring data.
- Model accuracy and assumptions were evaluated against *in vivo* data to determine appropriate context for use, given tissue, chemical properties, and desired accuracy.
- We used a simulation study to evaluate the impact of tissue lumping and negligible blood volume and compared generic perfusion-limited PBTK model predictions to one- and two-compartment models.
- 427 compounds were simulated with a PBTK model using oral dosing to evaluate model assumptions, and in a separate analysis,1446 *in vivo* measurements were used to evaluate partition coefficients and volume of distribution.



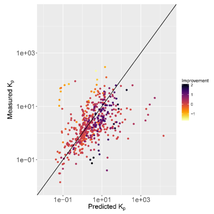
HTTK R Package

- httk (high-throughput toxicokinetics) is an R package (https://cran.r-project.org/web/packages/httk/index.html) for solving toxicokinetic models and predicting model outputs and parameters such as steady state concentration, maximum concentration, elimination rate, area under the curve (AUC), clearance, partition coefficients, and volume of distribution.
- Generic model structures are tailored to specific chemicals using physcio-chemical descriptors and the results of in vitro experiments. The in vitro experiments characterize intrinsic hepatic clearance and plasma protein binding (F_{ub}) of the parent compound.
- Partition coefficients were calculated with a modification of the Schmitt 2008 model whose general form is shown in the figure: These modifications include changes to membrane affinity prediction and *in vitro* F_{ub}.
- A future release of httk, version 1.6, will contain the changes in partitioning used here.
- The volume of distribution is calculated by summing the partition coefficients, multiplied by their volumes:

$$V_{dist} = \sum_{tissues} K_p V_{tissue} + V_{plasma}$$



httk simulates single and multiple dosing schemes. This plot show 3 doses per day of 1 mg/kg/day of Bisphenol-A in a human.



Rat partition coefficients predicted with new membrane affinity predictor shown above with improvement shown in orders of magnitude.

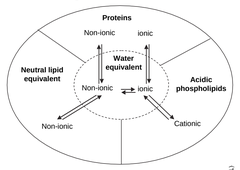
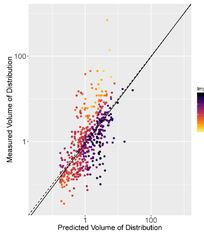


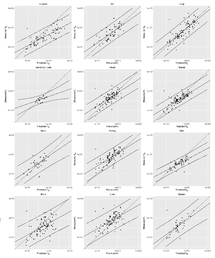
Figure from Peyret 2010

Chemical-specific TK models can be created rapidly using *in vitro* assays and computational approaches.

Partition Coefficients

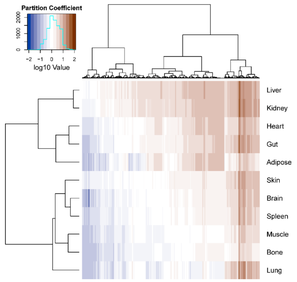
Partition coefficient error is tissue specific. Tissues rich in neutral lipid such as brain and adipose generally had larger predictions than measurements. Predicted rat K_p in the figure on the right were regressed on *in vivo* data after a modification of the model of Schmitt 2008.





Human volume of distribution predictions, shown on the left, were predicted with membrane affinity and F_{ub} corrections and a further calibration, shown above. Improvement (see color legend) is defined as the decrease in the absolute value of the error, measured in orders of magnitude, after regression calibrations.

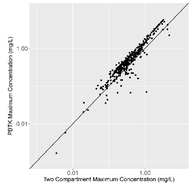
Chemical and Tissue Similarity



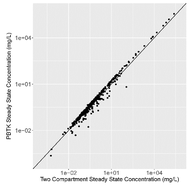
856 corrected and calibrated human partition coefficient predictions form three general clusters of low, medium, and high partitioning. From low to high, these are hydrophilic acids, lipophilic neutrals, and lipophilic bases.

1 and 2 compartment vs PBTK

- The 2 compartment model more accurately replicated the PBTK model than the 1 compartment model.
- A two compartment model was created that was equivalent to a one compartment model with a separate liver compartment with additional kidney clearance.
- Peak and steady state concentrations, elimination, and distribution phase duration for the 2 compartment model were observed to be mostly within a factor of 2 of the PBTK model for all 427 compounds.



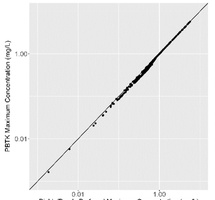
Peak concentration was the largest difference between the 2 compartment and pbtk models.

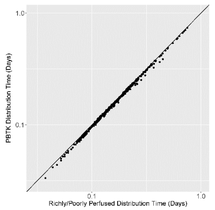


The 2 compartment model predicted steady state for rapidly cleared compounds significantly better than the 1 compartment model.

Richly/Poorly Perfused Tissue

- Unnecessary to separate richly and poorly perfused tissues.
- Assuming negligible blood volume and lumping together richly and poorly perfused tissues was shown to have little affect on the model outputs.
- Spleen, brain, and heart were considered richly perfused while adipose, bone, muscle, and skin were considered poorly perfused.

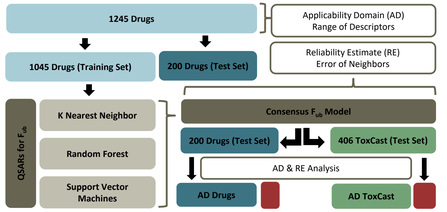


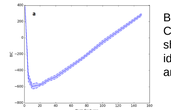


- We considered peak and steady state concentrations, elimination, and distribution phase duration.
- The peak concentration after separating the rest-of-body compartment into separate richly and poorly perfused compartments was the largest difference, all values still well within a factor of 2.

In Silico Prediction of HTTK Parameters

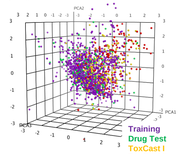
- QSAR for fraction of chemical unbound to plasma protein (F_{ub}) built with *in vitro* human plasma protein binding assays (pharmaceuticals and ToxCast chemicals) is a generalized model ideal for toxicokinetic studies.
- Component QSAR models contain 10-15 2D descriptors, with metrics for hydrophobicity, aqueous solubility and charge highly ranked in each.
- Bounded box and principal component analysis outline an applicability domain (AD). 3D reliability estimate based on similarity to training set, deviation between individual predictions, and F_{ub} prediction value.
- Excellent predictions in neutrals and acids, the charged state most commonly found in ToxCast.
- F_{ub} predictions for ToxCast chemicals are better than those for pharmaceuticals. ToxCast chemicals largely within the AD.





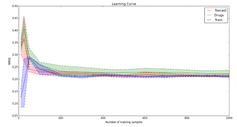
Bayesian Information Criterion (BIC) curve shows 10-15 descriptors ideal balance of accuracy and simplicity.

Principal component analysis shows overlap in key chemical space of pharmaceuticals and ToxCast chemicals.



F_{ub} QSAR prediction quality metrics

	Pharmaceuticals		ToxCast	
Method	MAE	RMSE	MAE	RMSE
kNN	0.164	0.242	0.136	0.221
SVM	0.177	0.251	0.146	0.216
RF	0.157	0.231	0.119	0.211
Con	0.155	0.225	0.122	0.196



Learning curves show >300 pharmaceutical training set can predict F_{ub} for ToxCast well.

Conclusion

- Adding the additional complexity of realistic blood volumes and separating the rest-of-body compartment into richly and poorly perfused compartments had little affect on the model predictions. The most significant change was the increase in peak concentration with the richly/poorly perfused correction.
- The tissue of interest, ionization, and lipophilicity displayed distinct partitioning classes.
- The use of a PBTK model is generally equivalent to one- and two-compartment models. The two-compartment model was generally more similar to the PBTK, but the 1 compartment model more closely corresponded to the PBTK for compounds with slower elimination (< 0.5 /h). For compounds with greater elimination, the 1 compartment model predicted an overly rapid elimination and thus lower steady state as well as a very high Cmax relative to the PBTK.
- We recognize these models may require the addition of diffusion-limited, transporter-mediated, and saturable processes as well as further comparison using a greater diversity of dosing methods and compounds.

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