Developing Generic Toxicokinetic Models with R Package "httk" for Enhanced Reporting Accuracy and Statistical Evaluation

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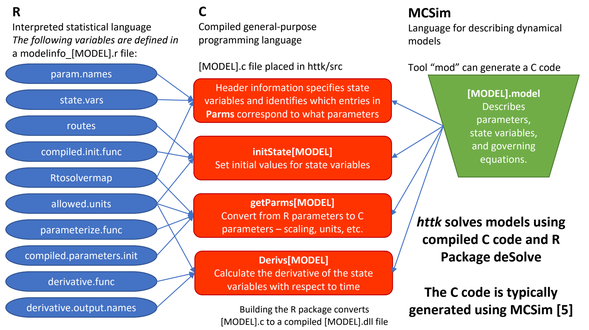
Introduction

- Decisions about the risk posed by a chemical to the public health involve models for toxicity, exposure, and the dose-response relationship. Toxicokinetics (TK) informs the dose-response relationship by describing the absorption, distribution, metabolism, and excretion (ADME) of a chemical dose
- The "*httk*" R package (https://cran.r-project.org/package=httk) [1] informs *in vitro-in vivo* extrapolation (IVIVE) for chemical risk assessment by providing both chemical-specific *in vitro* data for predicting TK and a suite of "generic" models (including PBTK) that use those data to predict ADME.
- The ***high throughput toxicokinetics (httk)*** environment addresses three barriers to the incorporation of PBTK models into risk assessment in non-pharmaceutical regulatory settings [2]:
  1) **Data availability** (that is, lack of clinical trials): *httk* provides access to chemical-specific data and predictions for thousands of chemicals
  2) **Model reproducibility**: Despite the deterministic nature of scientific computing, it is often difficult to reproduce computational results [3]
  3) **Statistical evaluation**: New generic TK models can be evaluated across the growing library of chemicals with both *in vitro* and *in vivo* data

Here we discuss how new models may be created and interlaced with the *httk* environment, so that previously evaluated tools and data may be incorporated alongside new approaches

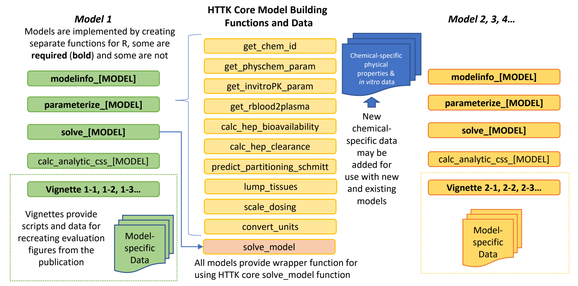
Integrating New Models

- ***httk* makes use of three open-source computer programming languages: R, MCSim, and C**
- Typical users and the *httk* design team use R [4], an interpreted statistical analysis language
- TK modelers can use MCSim [5] to describe new models and the MCSim function "mod" is then used to convert MCSim to C code that can be compiled for rapid execution by R
- Here we indicate the name of a new model (such as "gas_pbtk" or "fish_pbtk") with "[MODEL]"
- *httk* simulates the compiled C models with R package deSolve [6], using instructions provided by modelinfo_[MODEL].R
- **Once integrated a model can be used for TK ("calc_mc_tk()") and IVIVE ("calc_mc_css()")**



Generic Functions for TK Models

- ***httk* is intended to permit flexibility with respect to the description of toxicokinetics but allows the reuse of data and tools for tasks such as parameterization, unit conversion, and Monte Carlo simulation**
- By using pre-existing, peer reviewed, and publicly vetted data and code we aim to minimize errors in physiology, chemistry, calculation, and implementation – "Do things once"
- For example, we have a single function for conversion of units (such as µM to mg/L) called "convert_units()" and reuse it wherever needed to minimize the chances of making a mistake



Parameter Tables

- **Models developed for the *httk* suite are designed to be used to make chemical-, species-, and tissue-specific predictions, drawing from data tables provided with the R package**

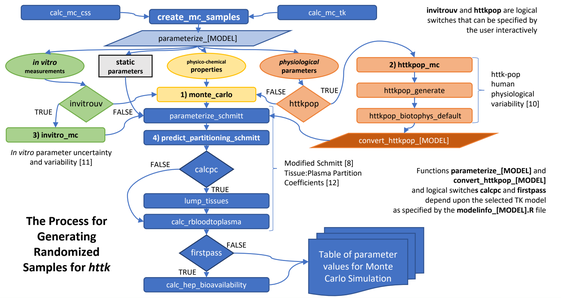
Tables available within *httk*

chem.physical_and_invitro.data	Chemical-specific values for physico-chemical properties and *in vitro* measurements
chem.invivo.PK.data	Chemical concentration vs. time data (CvTdb) for evaluating model predictions [7]
physiology.data	Species-specific physiological parameters, currently covering human, monkey, rat, rabbit, and mouse
tissue.data	Tissue composition data for Schmitt's method of partition coefficient prediction [8]
Tables.Rdata.stamp	Time stamp identifying when the other tables were created

- Over the past decade EPA, its collaborators, and its contractors have made chemical-specific measurements of *in vitro* TK determinants (largely plasma protein binding and intrinsic hepatic clearance) for over 1,200 chemicals in humans and more than 200 chemicals in rats
- Additional chemical-specific data as well as physiological information and tissue-descriptors have been curated from the scientific literature
- Physico-chemical properties are predicted with the OPERA quantitative-structure-activity relationship (QSAR) suite [9]

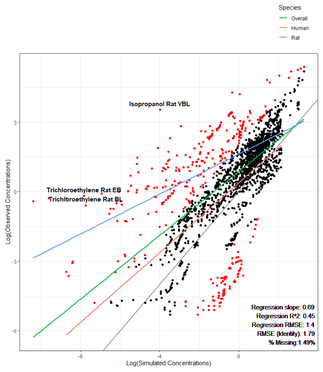
Monte Carlo

- ***httk* propagates both uncertainty and variability with Monte Carlo (MC) simulation**
- "create_mc_samples()" is the primary function and creates a table of samples with a column for each parameter and a row for each "draw" of the MC simulation
- Population variability in physiological parameters is controlled by function "httkpop_mc()" [10], while measurement uncertainty and population variability in chemical-specific parameters is controlled by "invitro_mc()" [11]
- Since httk-pop predicts correlated human population variation in more than 50 biometrics [10], modelers may include a custom function "convert_httkpop_[MODEL]()" to relate those parameters to their PBTK model
- For rapid Monte Carlo it is recommended that modelers develop an analytical steady-state solution for their model ("calc_analytic_steadystate_[MODEL]()"



Model Evaluation Data

- **The most challenging task is not building a new model, but evaluating that model**
- Each new addition to *httk* should include an evaluation of model predictions relative to *in vivo* data where available (as in the table "httk::chem.invivo.PK.data" from CvTdb [7])
- Based on the outcome of your evaluation, it may be possible to estimate how generalizable the new model is expected to be
- Linakis et al. (2020) [13] added a generic gas inhalation PBTK model to *httk*, included in version 2.0.0. They estimated the root mean squared error (RMSE) for model predictions for 41 volatile organic chemicals in 143 inhalation exposure experiments drawn from the CvTdb [7] including exhaled breath (EB), blood (BL), and venous blood (VBL) data



Community Involvement

- Version control software is used by EPA and a public GitHub repository is maintained at: https://github.com/USEPA/CompTox-ExpoCast-httk
- Users of *httk* can use GitHub to identify bugs with functions, problems with data, and even submit suggested fixes
- Each release follows the R version numbering convention, with three numbers indicating: "Major Releases", "Minor Releases", and "Patches". The current version of is 2.0.4
  - Patches include relatively minor alterations of the functions and data to address problems identified by the scientific community
  - Minor releases always accompany peer-reviewed publications, and typically cover new models or data sets
  - A major release would involve restructuring most or all the underlying R code and none is currently planned

Conclusions

- All users can access the peer-reviewed data and functions of *httk*, however model developers can incorporate new models by developing a TK model description in the language MCSim and then using a modelinfo_[MODEL].R file to describe that model to *httk*
- An upcoming manuscript will describe this procedure in detail
- *httk* models allow transparency, portability, statistical evaluation, and community feedback

https://www.epa.gov/research/

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