A General Approach for Specifying Informative Prior Distributions for PBPK Model Parameters

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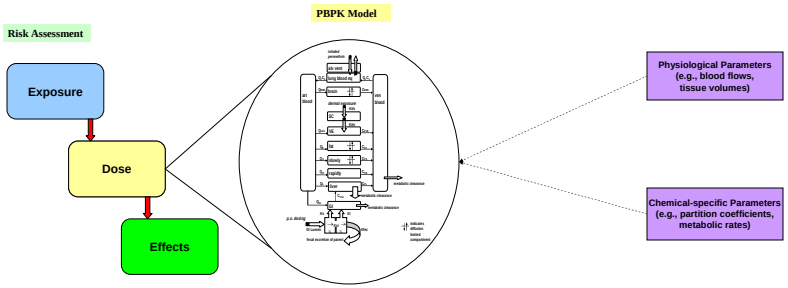
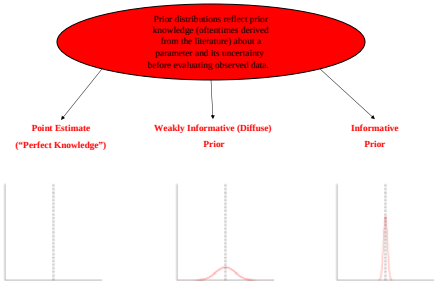
Abstract

Characterization of uncertainty in model predictions is receiving more interest as more models are being used in applications that are critical to human health. For models in which parameters reflect biological characteristics, it is often possible to provide estimates of parameters along with uncertainties even in the absence of experimental results against which to compare predictions. Thus, uncertainties for model predictions can be derived from such parameter uncertainty even when there are little or no *in vivo* data available. When appropriate data do exist, such *prior information* (or priors) can be incorporated into Bayesian statistical methods for parameter estimation. Informative priors are often used for physiological parameters in PBPK models to indicate how well-known these parameters are. However, chemical-specific parameters are often assigned vague or weakly informative priors due to much greater uncertainty in parameter values. We describe some approaches that can be used to specify more informative priors for chemical-specific parameters based on information obtained from computational predictors, such as QSAR models, *in vitro* assays, and data sets of measured parameters. In the approaches discussed here, predictions made by computations predictors or *in vitro* assays are compared to experimentally determined chemical-specific values for a selection of chemicals. Standard statistical methods (e.g., linear regression) are used to determine the (bias-adjusted) mean and variance, or coefficient of variation (CV), for the priors quantifying parameter uncertainty. CVs of 50 – 70% computed for various partition coefficients (PCs) with data from an in-depth literature survey demonstrate the validity of these approaches. These methods are also illustrated in an example evaluating the contribution of the uncertainty in PCs to overall PBPK model uncertainty.

Motivation

'Expert judgment' is often the norm for setting priors used in Bayesian analysis for model calibration, uncertainty and variability analyses, and model evaluation. However, this approach is not sufficiently transparent nor systematic enough for the regulatory application of setting health-protective exposure levels. Nor is it efficient for improving the underlying methods used to estimate model parameters. By developing a standard approach for setting priors we are able to more clearly delineate between diffuse priors and informative priors. Furthermore, a systematic treatment facilitates a closer dialogue between those scientists involved in parameter estimation and those employing parameters in models (e.g., PBPK models). The primary goal of this dialogue is to bring awareness to the need to describe the uncertainty in computed parameters used in models. Solely providing point estimates for model parameters does not suffice because of the ultimate need to specify uncertainties in model output predictions (such as in cumulative risk assessments).





Methods/Approach

• Goal: To develop a standard approach for the specification of informative priors (in particular, for chemical-specific parameters in PBPK models)

• What information is available in the literature that would be useful in setting informative priors?

• **Physiological Parameters**

  • Means and standard deviations (or coefficients of variation) for priors are typically found in the literature

• **Chemical-specific Parameters**

  • Experimental measurements of chemical-specific parameters

  • Computational predictors, such as QSAR and QSPR models, that predict parameters a priori

  • In vitro measurements of metabolism (for example, intrinsic clearance) that can be used to predict in vivo clearance

• **Approach:**
  • Use regression analysis to determine relationship (and correct bias) between experimental and predicted values
  • Mean for prior is given by the (regression corrected) predicted value
  • Standard deviation for prior is given by the root mean squared error (RSME)

Results

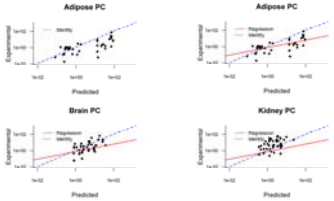
Partition Coefficients

Partition coefficients (PCs) are important PBPK model parameters because of their role in determining the distribution of a compound to various tissues throughout the body.

Schmitt's (2008) computational predictor for PCs takes into account the composition of the tissues, lipophilicity, binding to phospholipid membranes, pKa and unbound fraction of compound in blood plasma.

Regression of experimentally determined PCs on computational values is used to adjust for bias.

Regression analysis was carried out on the log scale with exneriementallv determined PCs obtained from the literature.

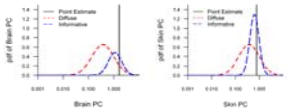


log Standard Deviations for Priors

Tissue	log SD	Tissue	log SD
Adipose	0.5423	Lung	0.9153
Brain	0.6093	Muscle	0.5751
Bone	0.597	Skin	0.4474
Gut	0.7169	Spleen	0.724
Heart	0.5766	Testis	0.414
Kidney	0.614	Thymus	0.2685
Liver	0.6926		

Example PCs Prior Distributions

Comparison of diffuse priors with log SD = 1.5 (red dashed line) to informative priors with log SD from table above (blue dashed line) with regression corrected Schmitt predicted PC value denoted as the point estimate



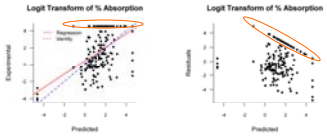
Oral Absorption Rates

Oral absorption rates (e.g., intestinal absorption rate constants and GI transfer rate constants) are also important PBPK model parameters because of their role in determining the absorption or uptake of chemicals in the body.

Zhao et al. (2003) developed a QSAR model based on linear regression that uses Abraham descriptors for the percentage of oral absorption in rats, which can be transformed to absorption rate constants via Yu et al. (199) compartmental absorption and transit model.

Linear regression was initially carried out on the logit transformed intestinal absorption data versus predictions from Zhao's model.

Model does a poor job of predicting values corresponding to 100% absorption.

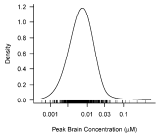


Alternative predictors for oral absorption rates (e.g., Caco-2 cell permeability) may provide better predictions and result in a more informative prior.

Permethrin PBPK Model Uncertainty

Informative prior distributions for partition coefficients via the proposed approach and for clearance rates based on *in vitro* data in Scollon et al. (2009) were used to demonstrate how uncertainty in PBPK model parameters contributes to the overall uncertainty in PBPK model predictions.

Using the PBPK model for permethrin developed by Tornero-Velez et al. (2010), simulations were performed for rats given an oral dose of 1 mg/kg of permethrin.



The probability density function (pdf) obtained for model predicted peak brain concentration demonstrates how uncertainty of in a *subset* of the PBPK model parameters can result in a considerable amount of uncertainty in internal dose.

Conclusions

• More informative prior distributions for Bayesian analysis of PBPK models can be developed with the use of appropriate computational predictors (e.g., QSAR and QSPR models), *in vitro* methods, and readily available data in the literature.

• Prior uncertainty in model parameters can be used to more accurately assess uncertainty in PBPK model predictions as opposed to predictions based on fixed point estimates or vague priors for model parameters.

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