

# The Rapid Generation of Physiologically Based Pharmacokinetic Models

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## INTRODUCTION

A reliable, scientifically-based and quantitative chemical risk assessment technique is the goal of governments and industry worldwide. Physiologically-based pharmacokinetic (PBPK) (Fig. 1) modelling is a powerful means of simulating the factors that determine tissue dose within any biological organism and consequently, correlation with health effects. The value of PBPK models is that they are tools for integrating *in vitro* and *in vivo* mechanistic, pharmacokinetic and toxicologic information through their explicit mathematical description of important anatomical, physiological and biochemical determinants of chemical uptake, disposition and elimination. Thus, PBPK modelling is a potential tool for use in risk assessment. However, PBPK models are perceived as complex, data hungry, resource intensive and time consuming. To address these issues a system for the rapid construction of PBPK models is under development. Currently, 'proofs of concept' for the essential components have been developed.

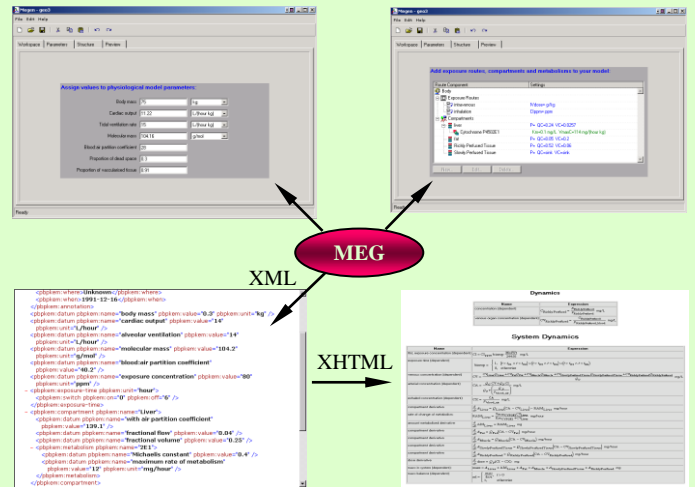
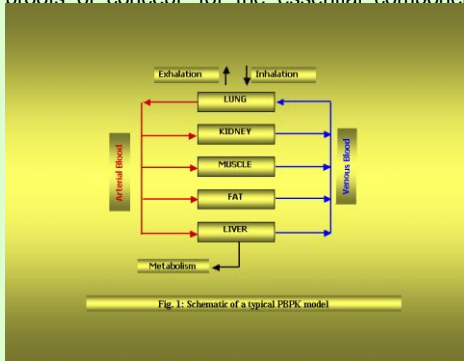


Fig. 3: Montage of MEG screenshots (parameters and model structure property pages) and outputs (XML and XHTML)

The code is saved in a format (native syntax) which is run using a commercial simulation package where it may be visualised and exercised (Fig 4)

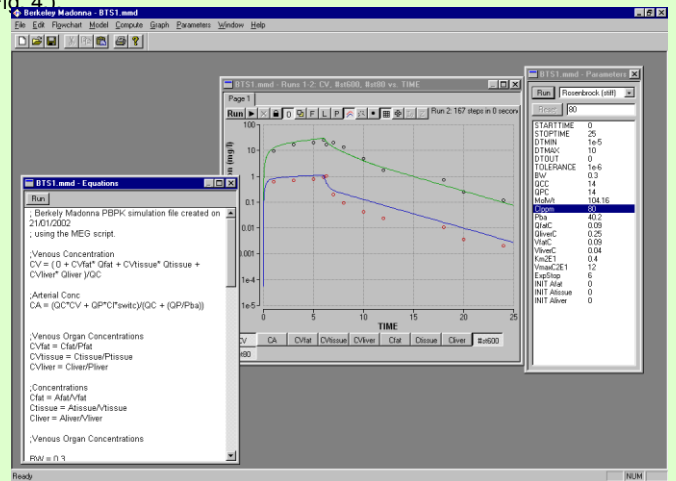


Fig. 4: Visualisation and exercise of model in a commercial simulation package

The modelling capability comprises two main components :

1. PBPK database
2. Model Equation Generator

### The PBPK Database

The anatomical, physiological, biochemical and physicochemical data required to build PBPK models will be entered into a specifically designed electronic database. Different values for parameters will be stored along with their source and an indication of the quality of the value. The aim is to make selection of all the parameters for a model easy and rapid. The output from the database will be in a form that will feed into the Model Equation Generator (MEG).

### The Model Equation Generator

The MEG is a stand-alone code generator that eliminates the need to formulate and code a set of equations. The user is engaged in a dialogue relating to the details of the physiology of the system to be modelled and the biochemistry and physicochemistry of the compound of interest. On the basis of this information, a script is produced in XML. The XML can be transformed into alternative markup (e.g. XHTML) or plain text for use in modelling software packages such as Berkeley Madonna and MCSim but could be produced in other formats for other modelling packages, such as ACSL and MATLAB.

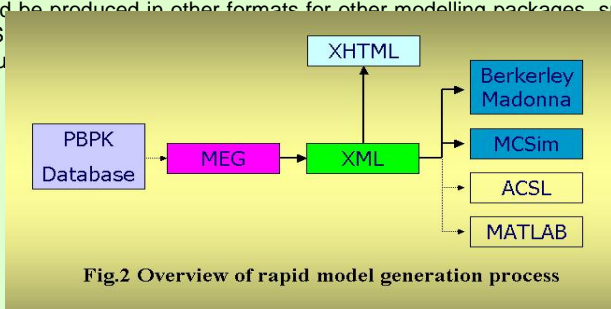


Fig.2 Overview of rapid model generation process

Figure 3 is a montage of screenshots showing 2 property pages from the MEG, the underlying XML code and mathematics viewed in XHTML in separate browser windows. The compartment volumes, blood perfusion rates, partition coefficients and metabolic rate constants are listed as the model is being constructed. The MEG transforms the mathematical

## SUMMARY

- Currently able to quickly generate and analyse standard PBPK models
- Shifts focus from mathematics to biology
- Saves time and money
- Massive scope for development

## FUTURE DEVELOPMENTS

- Interface with database. MEG will interrogate and extract parameters from database during model building process.
- Advanced statistical analysis of PBPK model output. Robustness of models and the uncertainty associated with parameters used must be quantified and justified. Therefore, appropriate and best tools for the statistical analysis of PBPK model parameters and outputs will be made readily accessible (e.g., Bayesian statistics and Markov chain Monte Carlo analysis)

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