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DoseSim: a tool for pharmacokinetic/pharmacodynamic analysis and dose reconstruction

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ABSTRACT

Summary: Assessing and improving the safety of chemicals and the efficacy of drugs depends on an understanding of the biodistribution, clearance and biological effects of the chemical(s) of interest. A promising methodology for the prediction of these phenomena is physiologically based pharmacokinetic/pharmacodynamic modeling, which centers on the prediction of chemical absorption, distribution, metabolism and excretion (pharmacokinetics) and the biological effects (pharmacodynamics) of the chemical on the organism. Strengths of this methodology include modeling across multiple scales of biological organization and facilitate the extrapolation of results across routes of exposure, dosing levels and species. It is also useful as the foundation for tools to (i) predict biomarker levels (concentrations of chemical species found in the body that indicate exposure to a foreign chemical), given a chemical dose or exposure; (ii) reconstruct a dose, given the levels of relevant biomarkers; and (iii) estimate population variability. Despite the importance and promise of physiologically based pharmacokinetic /pharmacodynamics-based approaches to forward and reverse dosimetry, there is currently a lack of user-friendly, freely available implementations that are accessible and useful to a broad range of users. *DoseSim* was developed to begin to fill this gap.

Availability: The application is available under the GNU General Public License from http://scb.colostate.edu/dosesim.html.

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1 INTRODUCTION

The rational design of drugs and drug dosing regimens, and the risk and safety assessment for environmental toxicants, depend on an understanding of the pharmacokinetics and pharmacodynamics (PK/PD) of the chemicals of interest. A methodology that is increasingly used for PK/PD analyses is physiologically based pharmacokinetic (PBPK) modeling (Reisfeld *et al.*, 2007). PBPK models integrate information across multiple time and spatial scales through the specification of biological, biochemical and physiological information at the tissue, organism and population levels. These models can then be used to predict the absorption, distribution, metabolism and excretion and potential biological effects of chemicals to the exposed individual. Moreover, through the use of appropriate parameter values, these models have the ability to extrapolate across doses, routes of administration and species.

The prediction of absorption, distribution, metabolism and excretion and biodistribution of the chemical and its metabolites, given an applied dose or exposure, is often known as *forward dosimetry*. The reverse case, in which biomarker levels are used to estimate the applied dose or exposure, is often known as *dose reconstruction* or *reverse dosimetry* (Lyons *et al.*, 2008).

Despite the increasing use of forward dosimetry and dose reconstruction in risk and safety assessment, few tools are available to conduct both types of analyses in an integrated manner. Moreover, the tools that are available are generally difficult to use by non-technical users and/or are proprietary.

To fill this gap, we developed the software framework *DoseSim*. The principal design objectives for this application were that it would (i) allow the user to perform forward dosimetry, forward dosimetry with Monte Carlo and dose reconstruction analyses; (ii) be easy to use for non-technical people; (iii) facilitate simple analyses and viewing of results without the need for additional software packages; (iv) allow alternative chemical-specific models to be used in this general framework; and (v) be freely available to the scientific and regulatory communities.

In this article, we describe the implementation, structure and features of DoseSim. *DoseSim:OP*, a specific application package [DoseSim plus a specialized PBPK/PD module focused on the analysis of binary mixtures of organophosphorus insecticides], is presented in Supplementary Information.

2 METHODS

DoseSim comprises a computational engine, a specific PBPK/PD model and a GUI layer. The computational engine behind the framework is MCSim (Bois, 2009) (https://www.gnu.org/s/mcsim/mcsim.html), a simulation package written in ANSI-standard C that facilitates the analysis of statistical or simulation models and performs Monte Carlo (MC) stochastic simulations and Bayesian inference through Markov chain Monte Carlo simulations. A number of changes were made to the publicly distributed version of MCSim (v5.1.0) to make it compatible with the structure and aims of DoseSim.

The underlying PBPK/PD models, generally consisting of systems of ordinary differential equations, were first written in the domain-specific language of MCSim (Bois, 2009) and were then compiled to C and linked to relevant libraries using MCSim utilities.

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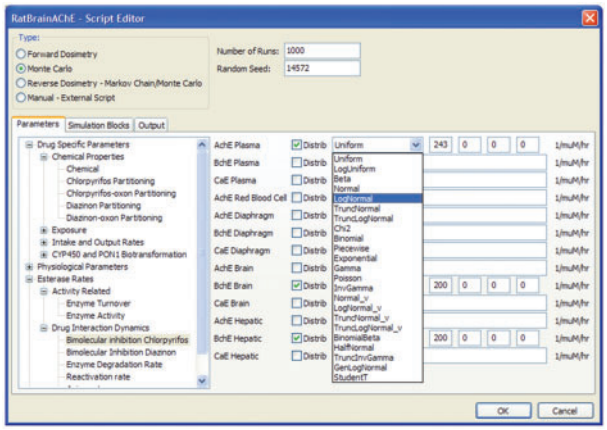

Fig. 1. Selecting the parameter distributions for MC analyses: a number of statistical distributions are available to the user through a drop-down menu

The DoseSim GUI and interface layer to MCSim were written in ISO/IEC2003 C++, making use of the wxWidgets library (v2.8.11). Statistical analyses of the simulation output were enabled using functions in the GNU Scientific Libraries, and plotting functionality was implemented using wxMathPlot. The various property sheets for parameter input are stored as XML and are automatically updated to accommodate changes in the underlying model structure. Project files are serialized as XML that can be modified outside of the GUI if desired.

Program Functionality: In DoseSim, the GUI interface allows easy simulation setup, running and analyses. Information is organized into *Projects*. Within a Project is one or more *Experiments*. Experiments are generally created, run and analysed using the following procedure: Begin a new Experiment and enter relevant parameters: The user selects the type of simulation and enters relevant parameters (or parameter distributions) through a tab-base interface (Fig. 1). Run the experiment: Once parameters and simulation sets have been input, the *Experiment*, which may comprise multiple simulations, is selected and run. View the results: Following completion of the simulation, results can be inspected and simulation results displayed in a variety of formats, including plots for MC simulations that display the envelope of the entire range of results along with mean values. Save and export the results: Following the simulations, results can be saved to the native XML format or exported to comma-separated value format for postprocessing, visualization and archiving with other tools.

3 DISCUSSION

3.1 Comparison with existing software

To our knowledge, there are no other software applications that fit the design objectives and needs noted earlier. A non-exhaustive list of applications that can be programmed to do at least forward dosimetry (+MC) and dose reconstruction simulations include the following: acslX (http://www.acslx.com/): proprietary software, command-line and GUI based. MATLAB (http://www.mathworks.com/products/matlab/index.html): proprietary software, command-line based, a selection of toolboxes for various types of analyses can be purchased from the vendor or downloaded from various repositories. MCSim (https://www.gnu.org/s/mcsim/mcsim.html): GNU General Public License, command-line based. R (http://www.r-project.org/): GNU General Public License, command-line based; a large selection of analysis and plotting packages can be obtained freely. WinBugs (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml): WinBUGS License, command-line based, several interfaces (Pharmaco, WBDiff) are available to extend the basic functionality. xmcsim (https://www.gnu.org/s/mcsim/mcsim.html): GNU General Public License, menu-driven GUI for MCSim (but requiring the installation of additional software).

Consistent with the design objectives described earlier, DoseSim has built-in functionality for forward dosimetry and dose reconstruction simulations and can perform simulations using a variety of statistical distributions. It is a GUI-driven application, containing familiar dialogs, widgets and spreadsheet-like grids for parameter and simulation specification. The interface contains flexible methods for specifying the dosing or exposure regimen and the sets of biomarkers for dose reconstruction simulations. Post-processing of results is facilitated through interactive plotting and convenient data export.

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Conflict of Interest: none declared.

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