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

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Abstract

Background

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 (PBPK/PD) modeling, which centers on the prediction of chemical ADME (absorption, distribution, metabolism, and excretion) and the biological effects of the chemical on the organism. A strength of this methodology is that it allows the inclusion and integration of various forms of information across multiple scales of biological organization and facilitates 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 given a chemical dose or exposure (forward dosimetry), (ii) reconstruct a dose given the levels of relevant biomarkers (reverse dosimetry), and (iii) estimate population variability. Despite the importance and promise of PBPK/PD-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.
Results

The DoseSim framework has built-in functionality for forward dosimetry, forward dosimetry with Monte Carlo (MC), and dose reconstruction simulations using a variety of statistical distributions. It is a user-friendly application with a graphical user interface (GUI) that employs familiar dialogs and widgets for parameter and simulation specification. The GUI also 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 integrated statistical analyses and interactive plotting. Finally, users are allowed to use, modify, and share the code in accordance with the GNU General Public License. Using the flexible DoseSim structure, the first application package, DoseSim:OP, was developed to analyze the ADME and pharmacodynamics of mixtures of organophosphorus insecticides.

Conclusions

DoseSim provides an extensible framework to conduct a wide variety of dosimetry studies. By incorporating relevant biological, biochemical, physiological, and anatomical information and data into the underlying model, the tool can provide the user with valuable insights into the ADME and effects of foreign chemicals on human health. We anticipate that chemical-specific application packages utilizing this framework, such as DoseSim:OP, will provide an important tool to inform studies related to drug disposition and safety and environmental chemical risk.

Background

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 [1]. 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 [2–4]. These models can then be used to predict the ADME (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 [5–7].

The prediction of ADME and biodistribution of the chemical and its metabolites given an applied dose or exposure is often known as forward dosimetry [8]. The reverse case, in which biomarker (e.g., the parent
chemical and/or its metabolites) levels are used to estimate the applied dose or exposure, is often known as *dose reconstruction* [9] or *reverse dosimetry* [10]. This type of analysis often relies on the application of Bayesian inference, where the PBPK/PD model is used as part of the likelihood function and the results (posterior distributions) are obtained via Markov chain Monte Carlo methods [11–13].

Despite the increasing use of forward dosimetry and dose reconstruction in risk and safety assessment [10–12,14–16], few tools are available to conduct both types of analyses in an integrated manner. Moreover, the tools that are available [17–21] 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 paper, we describe the implementation, structure, and features of DoseSim and illustrate specific results for *DoseSim:OP*, a specific application package (DoseSim plus specialized PBPK/PD module) focused on the analysis of binary mixtures of organophosphorus (OP) pesticides and insecticides.

**Implementation**

DoseSim comprises a computational engine, a specific PBPK/PD model, and a GUI layer.

The computational engine behind the framework is MCSim [19], 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 (MCMC) 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. Significant changes were as follows: (i) the error handling was modified to reduce the probability of program crashes and to assure that exceptions were propagated through the GUI layer in DoseSim, (ii) several enhancements were made to the input parser to allow additional parameters to be included in the simulations, (iii) the build system and some associated files were modified to increase cross-platform compatibility, and (iv) the pseudo-random number generator (PRNG) was changed to use the Mersenne twister algorithm [22], a PRNG with a much longer period and better statistical properties.

The underlying PBPK/PD models, generally consisting of systems of ordinary differential equations, were first written in the domain specific language of MCSim [23] and were then compiled to C and linked to
relevant libraries using MCSim utilities [23].

The DoseSim GUI and interface layer to MCSim were written in ISO/IEC2003 C++, making use of the wxWidgets library (v2.8.11) [24]. Statistical analyses of the simulation output were enabled using functions in the GNU Scientific Libraries [25] and plotting functionality was implemented using custom classes implemented using wxMathPlot [26]. 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.

Results and Discussion
Program Functionality

In DoseSim, information is organized into Projects. Within a Project is one or more Experiments. Each Experiment comprises a simulation specification (the type of simulation along with particulars for each run) and a set of user-specified or default chemical, biochemical, physiological, and anatomical parameters. After the simulation and analyses are run, resulting outputs and various user-generated plots are added to the Experiment. Experiments may be cloned to serve as baselines for related studies and multiple Experiments can be navigated and viewed through the tree-like Resource Explorer.

Experiments are generally created, run, and analyzed using the following procedure:

Begin a new Experiment and enter relevant parameters: The user selects the type of simulation [Forward dosimetry, Monte Carlo analysis (Forward dosimetry with MC), Dose reconstruction] and enters relevant parameters (or parameter distributions) through a tab-base interface. The base Parameters tab is specific for values related to drug and chemical properties, dosing and exposure specifications, physiological characteristics, statistical values, and biochemical properties (Figure 1). For MC and MCMC simulations, these values may be distributions (Figure 2). For dose reconstruction studies, there are special input facilities for biomarker values and likelihoods (Figure 3). The Simulation tab allows input about the various simulations to be run in a given experiment (Figure 4). The Output tab is for the specification of desired simulations outputs (Figure 5). These outputs can include any of the states, inputs, and parameters or functions of these variables.

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 (Figure 6) in a variety of formats (line plot, scatter plot, histogram, combination plots),
including plots for Monte Carlo simulations that display the envelope of the entire range of results along with mean values (Figure 7).

**Save and export the results:** Following the simulations, results can be saved to the native xml format or exported to csv (comma-separated value) format for postprocessing, visualization, and archiving with other tools.

**Comparison to 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 fitting several of the criteria is as follows:

- **acsIX [17]** proprietary software; command-line and GUI based; forward dosimetry (+ MC) and dose reconstruction simulations can be programmed using the Continuous Simulation Language (CSL)

- **MATLAB [18]** 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; forward dosimetry (+ MC) and dose reconstruction simulations can be programmed in the MATLAB language

- **MCSim [19]** GNU General Public License; command-line based; forward dosimetry (+ MC) and dose reconstruction simulations can be programmed using the MCSim language

- **R [20]** GNU General Public License; command-line based; very large selection of analysis and plotting packages that can be obtained freely; forward dosimetry (+ MC) and dose reconstruction simulations can be programmed using the R language

- **WinBugs [21]** WinBUGS License; command-line based; several interfaces (Pharmaco, WBDiff) are available to extend the basic functionality; forward dosimetry (+ MC) and dose reconstruction simulations can be programmed using the BUGS language

- **xmcsim [19]** GNU General Public License; menu driven GUI for MCSim (but requiring the installation of additional software); forward dosimetry (+ MC) and dose reconstruction simulations can be programmed using the MCSim language

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. Finally, users are allowed to use, modify, and share the code in accordance with the GNU General Public License (GPL).

**Planned Future Development**

Future development will focus in several areas: (i) creation of application packages (like DoseSim:OP based on an underlying PBPK/PD model from [27]) focused on specific chemicals and chemical mixtures of interest, (ii) enhancement and expansion of the documentation and example files, (iii) restructuring of the underlying computational engine to support parallel processing, and (iii) enabling Python [28] scripting for customized analysis and plotting capabilities.

**Conclusion**

The capability to predict the ADME and physiological effects of chemicals, and to characterize the biomarkers associated with chemical administration and exposure, are crucial in assessing the safety and efficacy of drugs and the toxicity of environmental toxicants. PBPK/PD modeling in the context of forward and reverse dosimetry is a promising methodology to address this need and integrate various forms of information across multiple scales of biological organization [29, 30]. Unfortunately, there is currently a lack of user-friendly, freely available applications that implement this methodology in a package that is accessible and useful to a broad range of users.

DoseSim provides a software framework to fill this need. This framework includes built-in functionality for forward dosimetry, forward dosimetry with MC, and dose reconstruction simulations built upon chemicalspecific PBPK/PD models. It has a graphical user interface with familiar dialogs and widgets for creating, running, analyzing, and visualizing a broad range of cases. For chemicals and chemical mixtures of interest, specific application packages, such as DoseSim:OP, can be created and distributed. Lastly, DoseSim is available under an open source license, allowing users to modify and share the code as needed in accordance with the terms of the GPL.

**Availability and requirements**

**Project name:** DoseSim

**Project home page:** http://scb.colostate.edu/dosesim.html
Operating system(s): Windows OS, Mac OS, Linux
Programming language: C++, C
Other requirements: none
License: GNU General Public License
Any restrictions to use by non-academics: none

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Figure 1: Specifying the simulation type and parameters: Parameters are chosen from a tree-like structure organized by type of input.
Figure 2: Selecting the parameter distributions for Monte Carlo Analyses: A number of statistical distributions are available to the user through a drop-down menu.
Figure 3: Setting the biomarkers and likelihoods for dose reconstruction: Biomarkers for chemicals of interest are entered (or copied) into a spreadsheet-like grid.
Figure 4: Defining the specifics of the simulation: Multiple simulations can be added to an Experiment and the inputs for each simulation are selected through a tree-like structure.
Figure 5: Choosing the desired outputs: Any of the state variables, parameters, or inputs can be selected as outputs, which can be then be analyzed, plotted, and stored.
Figure 6: Inspecting parameters and graphical simulation results: A number of plot types can be selected depending upon the application of interest. These types include, line, scatter, histogram, and combination plots. The variable(s) on the abscissa and ordinate are user selectable.
Figure 7: Viewing envelopes of solutions for Monte Carlo simulations: For Monte Carlo simulations, the extent and mean of the solutions can be easily visualized.
References


