Instructions for using source code and data files

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1. Unzip the file “Kapraun2020_naphthalene_pbpk_model.zip” to a folder on your C drive. For example, you could unzip to C:\Users\[username]\Documents to create a folder with the path “C:\Users\[username]\Documents\Kapraun2020_naphthalene_pbpk_model”.
2. Install R, RStudio, the R package “deSolve”, Rtools (optional), and MCSim (optional) on your system by following the instructions in the provided document “R_and_MCSim_installation_instructions.pdf”.
3. Open RStudio.
4. Within RStudio, open one of the R source code files in the “Kapraun2020_naphthalene_pbpk_model” directory. See “Description of files” below for information on the content and uses of each source code files.
5. Use the button in the upper right-hand corner of the window to “source” the file. Note that the “source” command causes a script to be read and interpreted by an R session instance (i.e., the “source” command “runs” a script).

Description of files:

- **build_naph_pbtk_2c.R**: This R source code file reads the file “naph_pbtk_2c.model” (an MCSim implementation of the two-compartment (2C) version of the naphthalene PBTK model) and creates the files “naph_pbtk_2c_model.c” (a C implementation of the model), “naph_pbtk_2c_model.o”, (a C object file), “naph_pbtk_2c_model_inits.R” (an R source code file that defines initialization functions for the model), and a compiled version of the model called either “naph_pbtk_2c_model.dll” (on a Windows system) or “naph_pbtk_2c_model.so” (on a Unix system) that can be used by the R package “deSolve”. This source code file reads and depends upon “RMCSim.R”. The files “naph_pbtk_2c_model.c”, “naph_pbtk_2c_model.o”, “naph_pbtk_2c_model_inits.R”, and “naph_pbtk_2c_model.dll” are included in this distribution, so it should not be necessary for Windows users to run “build_naph_pbtk_2c.R” unless they wish to modify and re-build the output files for “naph_pbtk_2c.model”.
- **build_naph_pbtk_pde.R**: This R source code file reads the file “naph_pbtk_pde.model” (an MCSim implementation of the partial differential equation (PDE) version of the naphthalene PBTK model) and creates the files “naph_pbtk_pde_model.c” (a C implementation of the model), “naph_pbtk_pde_model.o”, (a C object file), “naph_pbtk_pde_model_inits.R” (an R source code file that defines initialization functions for the model), and a compiled version of the model called either “naph_pbtk_pde_model.dll” (on a Windows system) or “naph_pbtk_pde_model.so” (on a Unix system) that can be used by the R package “deSolve”. This source code file reads and depends upon “RMCSim.R”. The files “naph_pbtk_pde_model.c”, “naph_pbtk_pde_model.o”, “naph_pbtk_pde_model_inits.R”, and “naph_pbtk_pde_model.dll” are included in this distribution, so it should not be

necessary for Windows users to run “build_naph_pbtk_pde.R” unless they wish to modify and re-build the output files for “naph_pbtk_pde.model”.

- **comp_skin_to_iv_exp.R**: This R source code file performs a simulation of skin and “background” (intravenous) exposure using the model “naph_pbtk_pde”. It then calculates the total amount of naphthalene absorbed through the skin (i.e., the total amount removed from the exposure well) and the total amount taken in due to the “background” (intravenous) exposure and prints results to the terminal.
- **human.R**: This R source code file defines an R function, “get_human_parms”, that sets model parameters relevant to human anatomy, physiology, and physical/chemical properties (with respect to naphthalene).
- **init_naph_pbtk_2c.R**: This R source code file loads the naphthalene PBTK model defined in the DLL file “naph_pbtk_2c.dll” (for Windows) or the SO file “naph_pbtk_2c.so” (for Unix). The script also loads all functions defined in the files “RMCSim.R” and “human.R”.
- **init_naph_pbtk_pde.R**: This R source code file loads the naphthalene PBTK model defined in the DLL file “naph_pbtk_pde.dll” (for Windows) or the SO file “naph_pbtk_pde.so” (for Unix). The script also loads all functions defined in the files “RMCSim.R” and “human.R”.
- **naph_pbtk_2c.model:** This MCSim source code file defines the two-compartment (2C) version of the naphthalene PBTK model.
- **naph_pbtk_2c_model.c**: This C source code file defines the two-compartment (2C) version of the naphthalene PBTK model.
- **naph_pbtk_2c_model.dll**: This DLL file defines the two-compartment (2C) version of the naphthalene PBTK model and can be used directly by functions in the R package “deSolve”.
- **naph_pbtk_2c_model.o**: This C object code file defines the two-compartment (2C) version of the naphthalene PBTK model.
- **naph_pbtk_2c_model_inits.R**: This R source code file defines initialization functions for the two-compartment (2C) version of the naphthalene PBTK model.
- **naph_pbtk_pde.model:** This MCSim source code file defines the partial differential equation (PDE) version of the naphthalene PBTK model.
- **naph_pbtk_pde_model.c**: This C source code file defines the partial differential equation (PDE) version of the naphthalene PBTK model.
- **naph_pbtk_pde_model.dll**: This DLL file defines the partial differential equation (PDE) version of the naphthalene PBTK model and can be used directly by functions in the R package “deSolve”.
- **naph_pbtk_pde_model.o**: This C object code file defines the partial differential equation (PDE) version of the naphthalene PBTK model.

- **naph_pbtk_pde_model_inits.R**: This R source code file defines initialization functions for the partial differential equation (PDE) version of the naphthalene PBTK model.
- **numerical_analysis.R**: This R source code file performs a simulation of skin and "background" (intravenous) exposure using the model "naph_pbtk_pde". It then computes the total mass of naphthalene in the system in two ways so that mass balance can be evaluated. It prints diagnostic information concerning mass balance to the terminal.
- **RMCSim.R**: This R source code file defines functions for compiling, loading, and running an ODE model encoded in the GNU MCSim model specification language. The "mod.exe" utility must be available in the user's PATH for the "compile_model" function to work properly.
- **sensitivity_analysis.R**: This R source code file performs a local sensitivity analysis for the model "naph_pbtk_pde". It creates plots and a CSV file that show local sensitivity indices for parameters in that model. Plots and the CSV file are saved in the "Output" directory.
- **skin_concentration_profile.R**: This R source code file performs a simulation of skin exposure using the model "naph_pbtk_pde" and uses the results to produce plots show skin concentration profiles (i.e., concentrations at various depths in the stratum corneum) for various points in time during the simulation. Plots are saved in the "Output" directory.
- **skin_exp_2c_fit_indiv.R**: This R source code file calculates an optimal set of parameters for the model "naph_pbtk_2c" for 10 subjects from the controlled JP8 skin exposure study of Kim et al. (2006). The optimization is performed using data from each of the 10 subjects independently. The results are stored in a data frame, which is then saved to the file "df_param_2c_indiv.rds" in the "Output" directory.
- **skin_exp_2c_plot_indiv.R**: This R source code file uses results from "skin_exp_2c_fit_indiv.R" that are saved in the file "df_param_2c_indiv.rds" in the "Output" directory. An optimal set of parameters for the model "naph_pbtk_2c" for 10 subjects from the controlled JP8 skin exposure study of Kim et al. (2006) is used to plot model simulated blood concentrations along with observed blood concentrations for each of the 10 subjects. Plot figures are saved to the "Output" directory in files with names of the form "skin_exp_2c_subjectXX_fit_indiv.tif" where "XX" is a number between 01 and 10 indicating the subject. Plot information is saved to the file "df_plot_2c_indiv.rds" in the "Output" directory. Summary statistical information for the optimal parameters, including mean and coefficient of variation, are also calculated and printed to the terminal.
- **skin_exp_pde_error_all.R**: This R source code file uses results from "skin_exp_pde_fit_all.R" that are saved in the file "df_param_pde_all.rds" in the "Output" directory. An optimal set of parameters for 10 subjects from the controlled JP8 skin exposure study of Kim et al. (2006) is used to calculate model-predicted blood concentrations for comparison with observed blood concentrations for each of the 10

subjects. Percent differences for raw concentrations and percent errors for difference-from-steady-state concentrations are calculated and summary information is printed to the terminal.

- **skin_exp_pde_fit_all.R**: This R source code file calculates an optimal set of parameters for the model "naph_pbtk_pde" for 10 subjects from the controlled JP8 skin exposure study of Kim et al. (2006). The optimization is performed using data from all 10 subjects simultaneously rather than optimizing independently for each subject. One parameter, HSCJP8, is assumed to be identical for all subjects. The results are stored in a data frame, which is then saved to the file "df_param_pde_all.rds" in the "Output" directory.
- **skin_exp_pde_fit_indiv1.R**: This R source code file calculates an optimal set of parameters for the model "naph_pbtk_pde" for 10 subjects from the controlled JP8 skin exposure study of Kim et al. (2006). The optimization is performed using data from each of the 10 subjects independently. The optimization is performed only for a single set of initial parameter values for each subject. The results are stored in a data frame, which is then saved to the file "df_param_pde_indiv1.rds" in the "Output" directory.
- **skin_exp_pde_fit_indiv2.R**: This R source code file calculates an optimal set of parameters for the model "naph_pbtk_pde" for 10 subjects from the controlled JP8 skin exposure study of Kim et al. (2006). The optimization is performed using data from each of the 10 subjects independently. The optimization is performed for multiple sets of initial parameter values for each subject. The results are stored in a data frame, which is then saved to the file "df_param_pde_indiv2.rds" in the "Output" directory.
- **skin_exp_pde_plot_all.R**: This R source code file uses results from "skin_exp_pde_fit_all.R" that are saved in the file "df_param_pde_all.rds" in the "Output" directory. An optimal set of parameters for the model "naph_pbtk_pde" for 10 subjects from the controlled JP8 skin exposure study of Kim et al. (2006) is used to plot model simulated blood concentrations along with observed blood concentrations for each of the 10 subjects. Plot figures are saved to the "Output" directory in files with names of the form "skin_exp_pde_subjectXX_fit_all.tif" where "XX" is a number between 01 and 10 indicating the subject. Plot information is saved to the file "df_plot_pde_all.rds" in the "Output" directory. Summary statistical information for the optimal parameters, including mean and coefficient of variation, are also calculated and printed to the terminal.
- **skin_exp_pde_plot_indiv.R**: This R source code file uses results from "skin_exp_pde_fit_indiv2.R" that are saved in the file "df_param_pde_indiv2.rds" in the "Output" directory. An optimal set of parameters for the model "naph_pbtk_pde" for 10 subjects from the controlled JP8 skin exposure study of Kim et al. (2006) is used to plot model simulated blood concentrations along with observed blood concentrations for each of the 10 subjects. Plot figures are saved to the "Output" directory in files with names of the form "skin_exp_pde_subjectXX_fit_indiv.tif" where "XX" is a number between 01 and 10 indicating the subject. Plot information is saved to the file "df_plot_pde_indiv.rds" in the "Output" directory. Summary statistical information for

the optimal parameters, including mean and coefficient of variation, are also calculated and printed to the terminal.

- **skin_exp_plot_compare.R**: This R source code file uses plot information saved in the files "df_plot_pde_indiv.rds, "df_plot_pde_all.rds", "df_plot_2c_indiv.rds" in the "Output" directory to plot three model simulated blood concentration trajectories along with observed blood concentrations for each of the 10 subjects. Plot figures are saved to the "Output" directory in files with names of the form "skin_exp_subjectXX_fit_compare.tif" where "XX" is a number between 01 and 10 indicating the subject.
- **skin_exp_plot_compare_all.R**: This R source code file uses plot information saved in the files "df_plot_pde_indiv.rds, "df_plot_pde_all.rds", "df_plot_2c_indiv.rds" in the "Output" directory to plot three model simulated blood concentration trajectories along with observed blood concentrations for each of the 10 subjects. A single multi-panel plot figure is saved to the "Output" directory in the file "skin_exp_fit_compare_all.tif".
- **skin_exp_sim.R**: This R source code file defines a function that can perform a model simulation of skin exposure based on the controlled JP8 skin exposure study of Kim et al. (2006). The function assumes that "load_model" (defined in "RMCSim.R") has been run with the appropriate model name so that the functions "initParms" and "initStates" are appropriately defined.
- **Data**: A directory containing two files, "kim_blood_data.csv" and "kim_subject_data.csv", which contain raw data from the study of Kim et al. (2006).
- **Output**: A directory containing output files described in the file descriptions above.