Symbolic PBPK-PDE Modeling Using Open-Source Julia Tools

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Abstract

Objectives: Physiologically based pharmacokinetic (PBPK) models provide a mechanistic characterization of a drug's distribution in the body. Ordinary differential equations (ODEs) are used for most PBPK models in literature which ignore the spatial distribution of a drug. Spatial distribution, however, can be critical to understand the PK of some drugs like topical preparations, inhaled treatments, and antitumor therapies. As such, investigators have tried to combine PBPK models, represented as ODEs, with partial differential equations (PDEs) to capture the spatial component of drug distribution. PBPK-PDE models are, however, challenging to build. The current work demonstrates a framework to build PBPK-PDE models using the open-source Julia [1] package, ModelingToolkit.jl [2], which can symbolically represent equations and simplify PDE model coding and integration with ODEs. A PBPK-PDE model of naphthalene diffusion from the skin into the body is used as an example of framework.
Methods: The PBPK-PDE model used in this work was a simplified version of a previously published naphthalene PBPK-PDE model [3]. The PBPK model described the distribution of topically administered naphthalene from the skin compartment into the circulation and remaining compartments (lung, liver, fat, poorly perfused and richly perfused tissues). The skin compartment was dissected into an outer well where naphthalene was introduced, *stratum corneum* (SC), and viable epidermis (VE). The diffusion of naphthalene across the one-dimensional space of the SC was represented as a PDE. The Julia open-source package MethodOfLines.jl [4] was used to automatically discretize the PDE problem. Boundary conditions were set to equilibrium conditions between the well and the outermost layer of the SC and between the VE and the innermost layer of the SC.
Results: The PBPK-PDE model was able to characterize the diffusion of naphthalene in the different SC layers as well as its penetration into the systemic circulation following dermal administration. The concentration of naphthalene in each of the discretized one-dimensional SC space versus time was demonstrated.
Conclusions: A framework using the Julia open-source tool, ModelingToolkit.jl, was developed to build PBPK-PDE models in a simple and intuitive way. A naphthalene PBPK-PDE model was used as a proof-of-concept, while the framework was generally applicable to the variety of pharmacometric models where a spatial component was critical to understanding activity.

Methods

Model structure.

The PBPK-PDE model structure was based on the published naphthalene model that characterized the PK of inhaled and topical naphthalene administration (Figure 1).

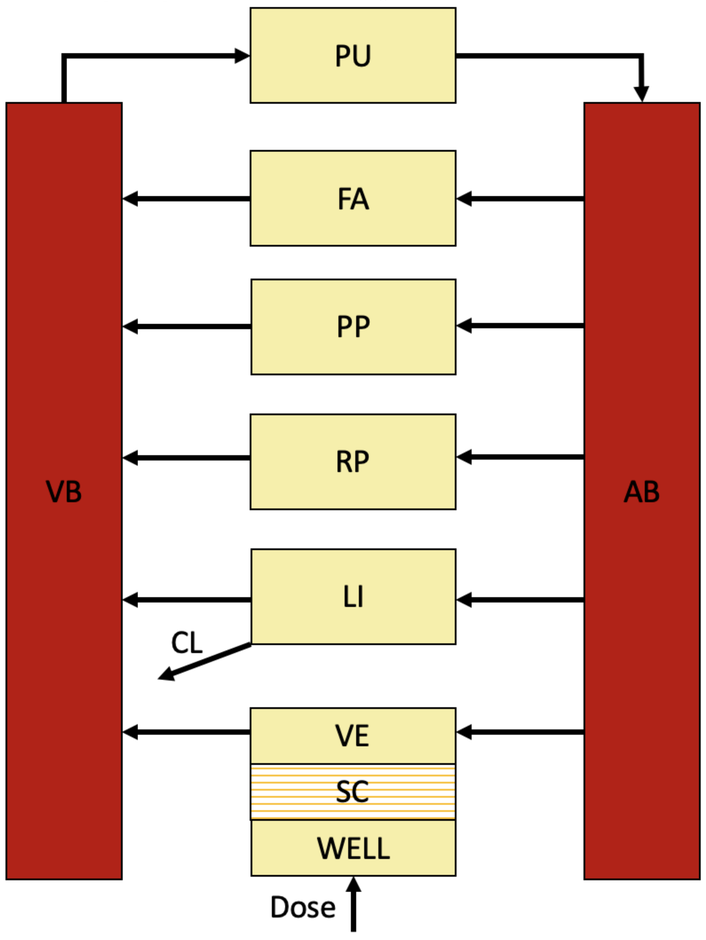

Figure 1. PBPK Model Structure. The PBPK model compartments were pulmonary (PU), fat (FA), poorly perfused (PP), rapidly perfused (RP), liver (LI), viable epidermis (VE), SC, arterial and venous blood tissues (AB and VB, respectively). WELL represented the topical naphthalene well. CL represented hepatic clearance. The SC was spatially stratified in the PDE component of the model.

Model equations.

The model equations included a set of flow-limited ODEs to describe the drug distribution between the different PBPK model compartments and PDEs to describe the drug distribution within the SC spatial layers.

ODEs

The distribution of the drug amount in VB was described by:

$$\frac{dA_{VB}}{dt} = Q_{LI}\frac{A_{LI}.H_{LB}}{VT_{LI}} + Q_{FA}\frac{A_{FA}.H_{FB}}{V_{FAT}} + Q_{RP}\frac{A_{RP}.H_{RPB}}{VT_{RP}} + Q_{PP}\frac{A_{PP}.H_{PPB}}{VT_{PP}} + Q_{VE}\frac{A_{VE}.H_{VEB}}{VT_{VE}} - QPU\frac{A_{VB}}{VT_{VB}},$$

where Q represents the tissue flow rate, VT represents the tissue volume, and H represents the tissue:blood partition coefficient for the respective tissue. QPU represents the sum of tissue flow rates for LI, VE, RP, PP, and FA.

PDEs

The concentration of drug in the SC $\varphi(x,t)$ was described by the following PDE:

$$\frac{\partial}{\partial t}\varphi(x,t) = D_{SC}\frac{\partial^2}{\partial x^2}\varphi(x,t),$$

with two boundary conditions defined at $x = 0$ (the outer surface of the SC in contact with the exposure well) and at $x = TSC$ (the maximum depth of the SC in contact with the VE)

$$\varphi(0,t) = H_{SC:JP8}C_{well}(t) \text{ and } \varphi(T_{SC},t) = H_{SC:VE}C_{VE}(t).$$

The parameter D_{SC} (cm^2/min) represents the diffusivity of naphthalene through the SC. $H_{SC:JP8}$ and $H_{SC:VE}$ represent partition coefficients between the SC and jet propulsion fuel (JP-8) and VE respectively. while $C_{well}(t)$ is the concentration of naphthalene in the exposure well while $C_{VE}(t)$ is the concentrations of naphthalene in the VE. The following initial condition at time $t = t_0$ was defined by

$$\varphi(x,t_0) = 0.$$

Packages

The following open-source Julia packages were used in the framework to build the integrated PBPK-PDE model:

- **ModelingToolkit.jl**. This package allows for the symbolic-numeric model representation.
- **MethodOfLines.jl**. This package allows for automatic discretization of space.

Results

A framework to build integrated PBPK-PDE models was developed with the open-source tool Julia and the packages ModelingToolkit.jl and MethodOfLines.jl. A case example with a published PBPK-PDE model for naphthalene was implemented (Figure 2). The framework was applied to simulate skin and "background" exposure (continuous intravenous dosing) with the integrated PBPK-PDE model. Continuous intravenous dosing of approximately 70 days was followed by skin exposure for 24, 36, 48, and 72 minutes. Following removal of skin exposure, continuous intraveneous dosing was administered for an additional five hours. The simulated concentrations of naphthalene in VB are visualized, demonstrating the increase in napthalene concentration due to skin exposure. Higher concentrations of naphthalene are observed with longer periods of skin exposure (Figure 3). The Julia framework was also used to demonstrate the ease of discretizing the SC into 10 spatial layers (Figure 4b). The simulated concentration of naphthalene in the SC due to dermal administration of 36 minutes from the open-source Julia framework is comparable to the simulated results from mrgsolve (Figure 4a). The framework allows for varying levels of discretizations based on the user's needs. The ease of discretizing the SC into 100 spatial layers was also demonstrated with the concentration of naphthalene simulated for the finer spatial discretization (Figure 5). The Julia framework can be easily extended and applied to a variety of spatial modeling components in pharmacometic applications, such as characterizing the distribution of antibody to the tumor and simulating inhaled drug particles through the airway (Figure 6).

Easy and compact implementation of multi-compartment PBPK model in Julia

```
@variables u(..) AWELL(t)=AWELLi AVE(t)=AVEi AAB(t)=AABi AVB(t)=AVBi ALI(t)=ALIi ATPU(t)=ATPUi ARP(t)=ARPi
APP(t)=APPi AFA(t)=AFAi

Dt = Differential(t)
Dx = Differential(x)
Dxx = Differential(x)^2

eqs = [
    Dt(u(t, x)) ~ DSC*Dxx(u(t, x)),
    Dt(AWELL) ~ DSC * Dx(u(t, 0))* AEXP,
    Dt(AVE) ~ -DSC * Dx(u(t, TSC)) * AEXP + QVE * ((AAB / VTAB) - ((AVE / VTVE) / HVEB)),
    Dt(AAB) ~ QPU * (((ATPU / VTPU) / HLUB) - (AAB / VTAB)),
    # updated for continuous intravenous dosing
    Dt(AVB) ~ QLI * (ALI / VTLI / HLB) + QFA * (AFA / VFAT / HFB) + QRP * (ARP / VTRP / HRPB) + QPP *
    (APP / VTPP / HPPB) + QVE * (AVE / VTVE / HVEB) - QPU * (AVB / VTVB) + infusion_rate,
    Dt(ALI) ~ QLI * ((AAB / VTAB) - (ALI / VTLI / HLB)) - VTLI * VmaxLI * (ALI / VTLI / HLB) / (KmLI +
    (ALI / VTLI / HLB)),
    Dt(ATPU) ~ -VTPU * VmaxLU * ((ATPU / VTPU) / HLUB) / (KmLU + ((ATPU / VTPU) / HLUB)) - QPU * ((ATPU /
    VTPU / HLUB) - AVB / VTVB),
    Dt(AFA) ~ QFA * ((AAB / VTAB) - (AFA / VFAT / HFB)),
    Dt(ARP) ~ QRP * ((AAB / VTAB) - (ARP / VTRP / HRPB)),
    Dt(APP) ~ QPP * ((AAB / VTAB) - (APP / VTPP / HPPB))
]

# initial and boundary conditions
bcs = [u(0.0, x) ~ u0,
u(t, 0.0) ~ HSCJP8 * AWELL / VWELL,
u(t, TSC) ~ HSCVE * AVE / VTVE]

# Space and time domains
domains = [t ∈ Interval(0.0, evtime),
           x ∈ Interval(0.0, TSC)]

pdesystem = PDESystem(eqs, bcs, domains, [t, x], [u(t, x), AWELL, AVE, AAB, AVB, ATPU, ALI, AFA, ARP, APP],
[]; name = name)
```

Figure 2. PBPK-PDE model implementation for naphthalene in Julia. The PBPK-PDE model equations for naphthalene along with the initial and boundary conditions were implemented using the open-source Julia package ModelingToolkit.jl.

Example simulation: impact of varied dermal exposure times on naphthalene blood concentration

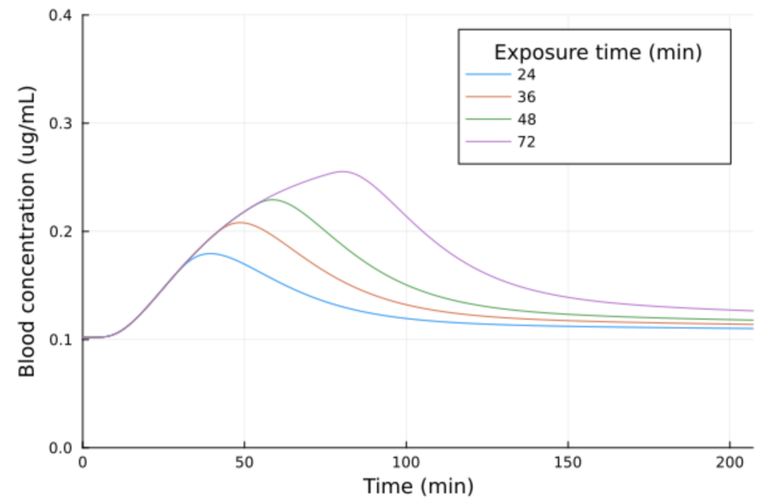

Figure 3. PBPK-PDE model simulation of naphthalene concentration in blood for various skin exposure times. The simulation results from the integrated PBPK-PDE model for naphthalene after 24, 36, 48, and 72 minutes of dermal administration illustrating the increase in naphthalene blood concentration due to diffusion through the skin with prolonged exposure.

Example simulation: discretization of SC into 10 spatial layers in Julia and mrgsolve

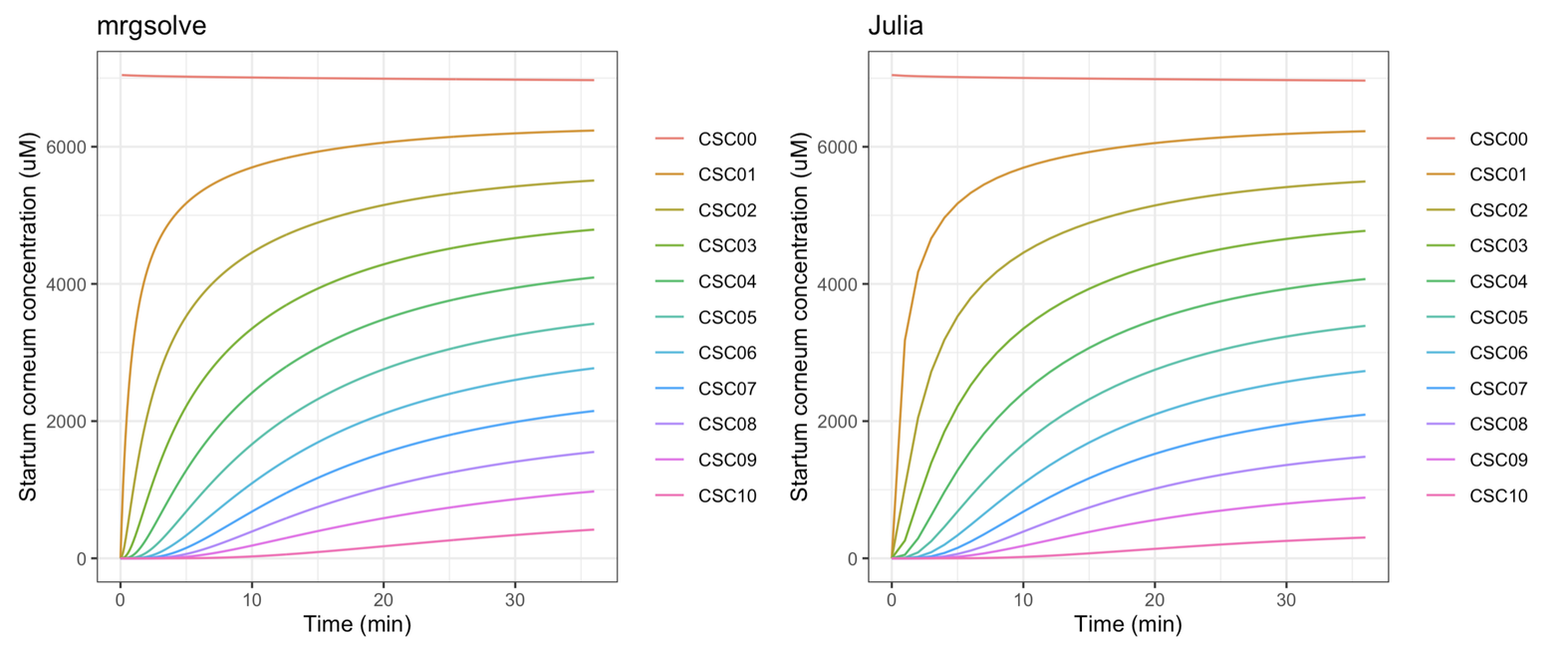

Figure 4. Julia and mrgsolve simulation of naphthalene concentration across 10 spatial layers in SC. The model simulation of the diffusion of naphthalene through 10 spatial layers of the SC depicted over time given dermal administration for 36 minutes using a) mrgsolve and b) the open-source Julia framework.

Example simulation: simple, intuitive code adaptation allows for finer discretization of 100 spatial layers

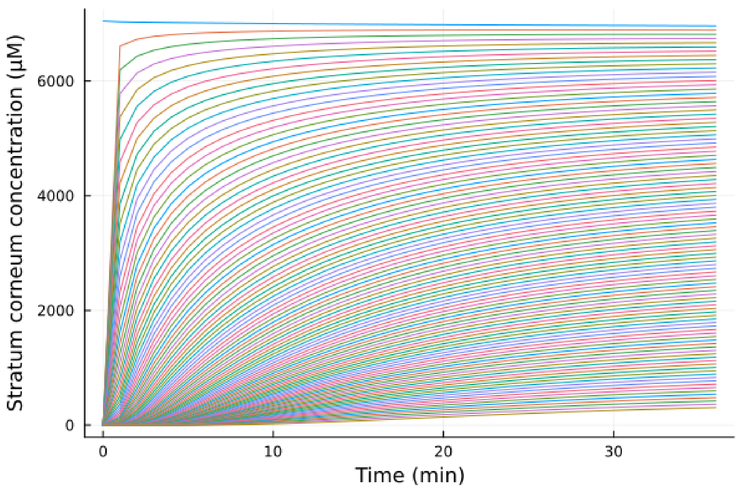

Figure 5. Naphthalene concentration across 100 spatial layers in SC. The simulated concentration of naphthalene in 100 spatial layers of the SC depicted over time given dermal administration for 36 minutes using the open-source Julia framework.

Julia framework is applicable to a variety of models with a spatial component

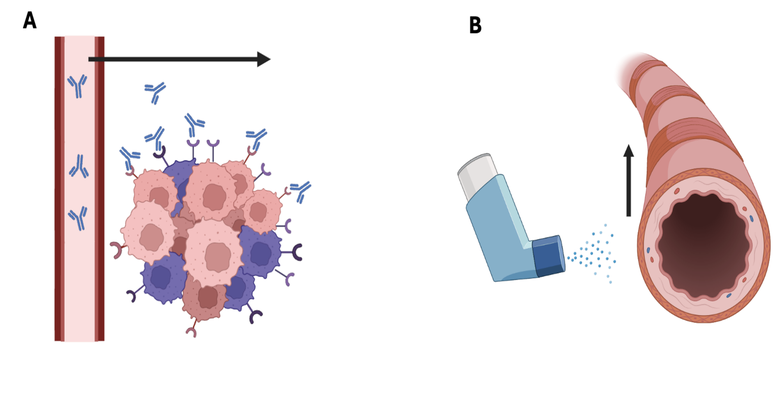

Figure 6. Pharmacometric modeling applications with a spatial component. The proposed Julia workflow could be used for spatial modeling in a) antibody distribution to the tumor and b) inhaled drug particles through the airway.

Conclusion

- In this work, a framework was demonstrated that seamlessly allows for the building of PBPK-PDE models using the Julia open-source tools: ModelingToolkit.jl and MethodOfLines.jl.
- The framework was demonstrated using the naphthalene PBPK-PDE model that characterizes the distribution of naphthalene through the spatial layers of the SC.
- The proposed framework is broadly applicable to various pharmacometric models where spatial components are crucial for understanding activity.

References

[1] Bezanson, J., Edelman, A., Karpinski, S. and Shah, V.B. Julia: A Fresh Approach to Numerical Computing. *SIAM Rev.* **59** (2017):65–98.

[2] Ma, Y., Gowda, S., Anantharaman, R., Laughman, C., Shah, V. and Rackauckas, C. ModelingToolkit: A Composable Graph Transformation System For Equation-Based Modeling (2021).

[3] Kapraun, D.F., Schlosser, P.M., Nylander-French, L.A., Kim, D., Yost, E.E. and Druwe, I.L. A Physiologically Based Pharmacokinetic Model for Naphthalene With Inhalation and Skin Routes of Exposure. *Toxicol. Sci.* **177** (2020):377–391.

[4] Creators Jones, Alex W. 1 Hyett, Criston Rackauckas, Chris2 Wellcome Trust Chan Zuckerberg Initiative (United States) Show affiliations 1. SciML 2. MIT. MethodOfLines.jl - Automatic finite difference PDE discretization and solving with Julia SciML.

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