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Open-Source Bayesian Hierarchical PBPK Modeling in Julia

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JuliaCon 07/27/2023

Objective

Demonstrate a Bayesian analysis workflow in Julia for an ODE-based model using PBPK modeling as an illustrative example.

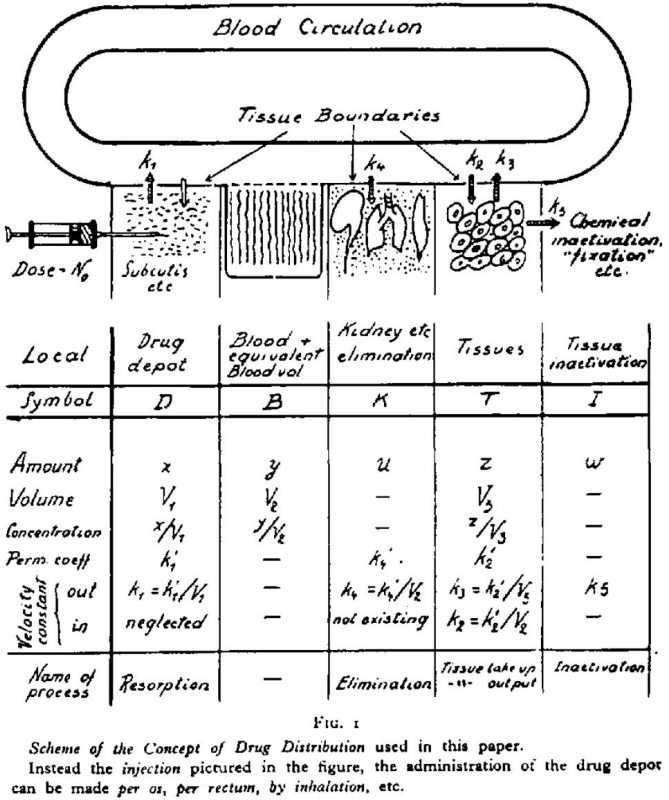
Introduction to PBPK Modeling - What is PBPK?

PB PK

<u>Physiologically based:</u>
Mechanistic approach that incorporates tissue structures and blood flows.

<u>Pharmacokinetics:</u>
What the body does to a drug (ADME: absorption, distribution, metabolism, excretion).

First introduced in 1937 by Torsten Teorell



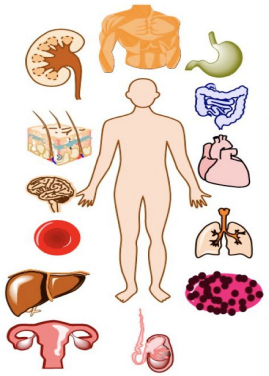
Local	Drug depot	Blood + equivalent Blood vol	Kidney etc elimination	Tissues	Tissue inactivation
Symbol	D	B	K	T	I
Amount	x	y	u	z	w
Volume	V_1	V_2	—	V_3	—
Concentration	x/V_1	y/V_2	—	z/V_3	—
Perm. coeff	k_1'	—	k_4' .	k_2'	—
Velocity constant out	$k_1 = k_1'/V_1$	—	$k_4 = k_4'/V_2$	$k_3 = k_2'/V_3$	k_5
Velocity constant in	neglected	—	not existing	$k_2 = k_2'/V_2$	—
Name of process	Resorption	—	Elimination	Tissue take up -"- output	Inactivation

FIG. 1

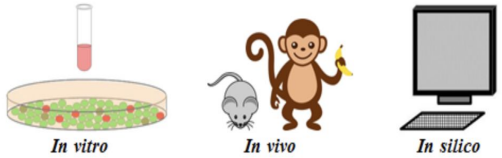
Scheme of the Concept of Drug Distribution used in this paper. Instead the *injection* pictured in the figure, the administration of the drug depot can be made *per os*, *per rectum*, *by inhalation*, etc.

Paalzow, Lennart K. (1995)

Introduction to PBPK Modeling - Structure



Deepika and Kumar (2023)

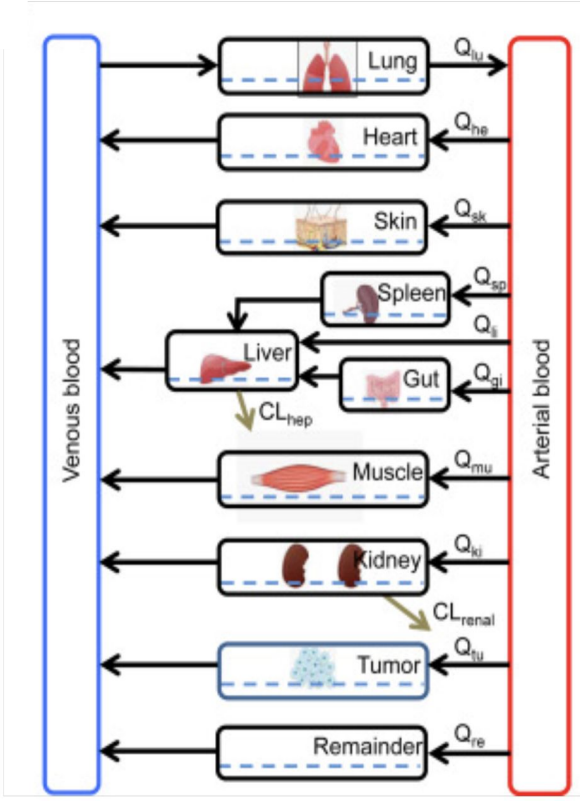


https://misciwriters.com/2016/10/04/in-silico-biology-how-math-and-computer-science-teach-us-about-life/

Physiological

Biochemical

$$\frac{dA_T}{dt} = Q_T\left(A_A/V_A - \frac{A_T/V_T}{Kp_T/BP}\right) - f_u.CL_T\frac{A_T/V_T}{Kp_T/BP}$$



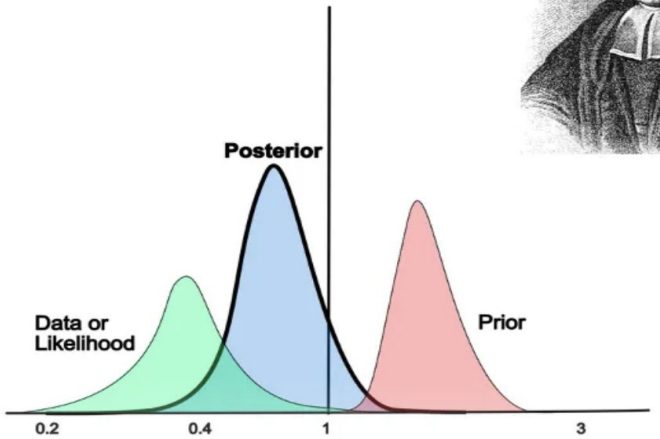
Adapted from Yuan et al. (2018)

Introduction to Bayesian Inference

- Bayesian inference is based on Bayes rule:

Likelihood Prior

Posterior $\longrightarrow$ $$p(\theta|y) = \frac{p(y|\theta).p(\theta)}{p(y)}$$ Marginal



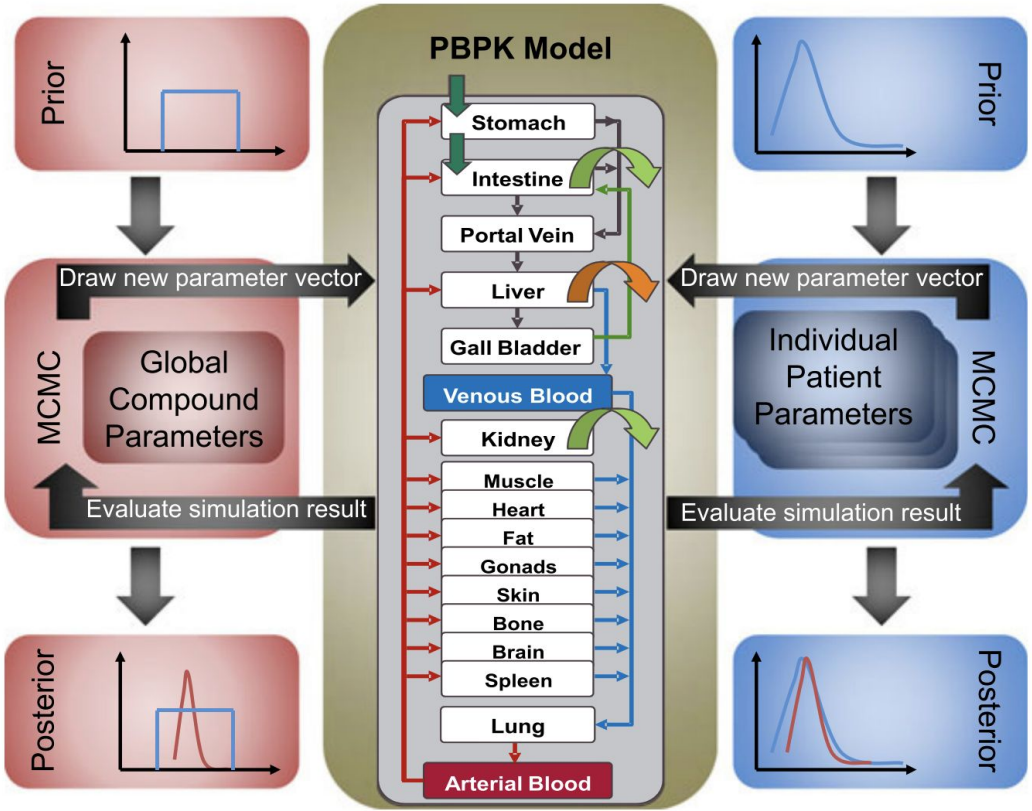
- Software landscape:
  - MCSim
  - BUGS
  - Stan/Torsten
  - Turing.jl
  - Soss.jl

https://www.cantorsparadise.com/an-actual-introduction-to-bayesian-statistics-96366fbf56f2

Why Bayesian PBPK?

- PBPK models are built based on the wealth of prior knowledge of the system and compound of interest.
- Bayesian inference updates prior knowledge with data.
- **Bayesian PBPK combines the best of both worlds since it uses the prior knowledge available on the system and compound and updates it with data while quantifying the uncertainty.**

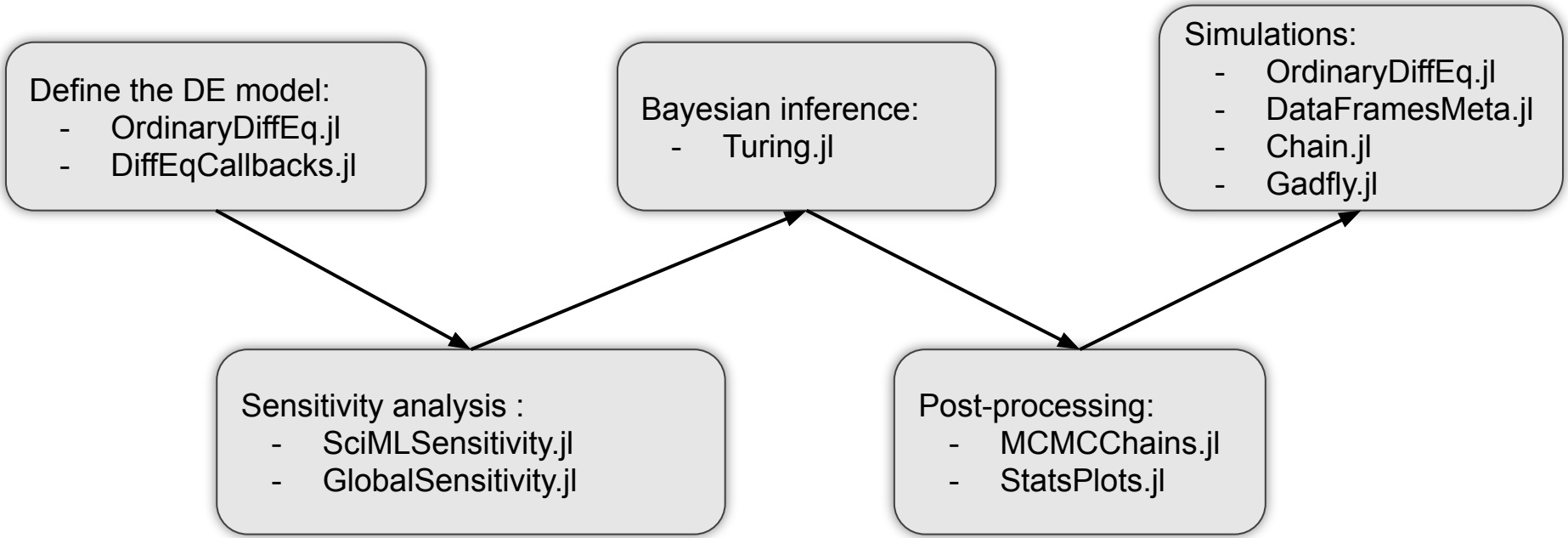
Bayesian PBPK Workflow



Krauss et al. (2013)

Why Julia?

- Solves the two-language problem.
- Open-source/traceability/reproducibility.
- Composability of the ecosystem.



Case Study

CPT: Pharmacometrics & Systems Pharmacology

TUTORIAL | Open Access

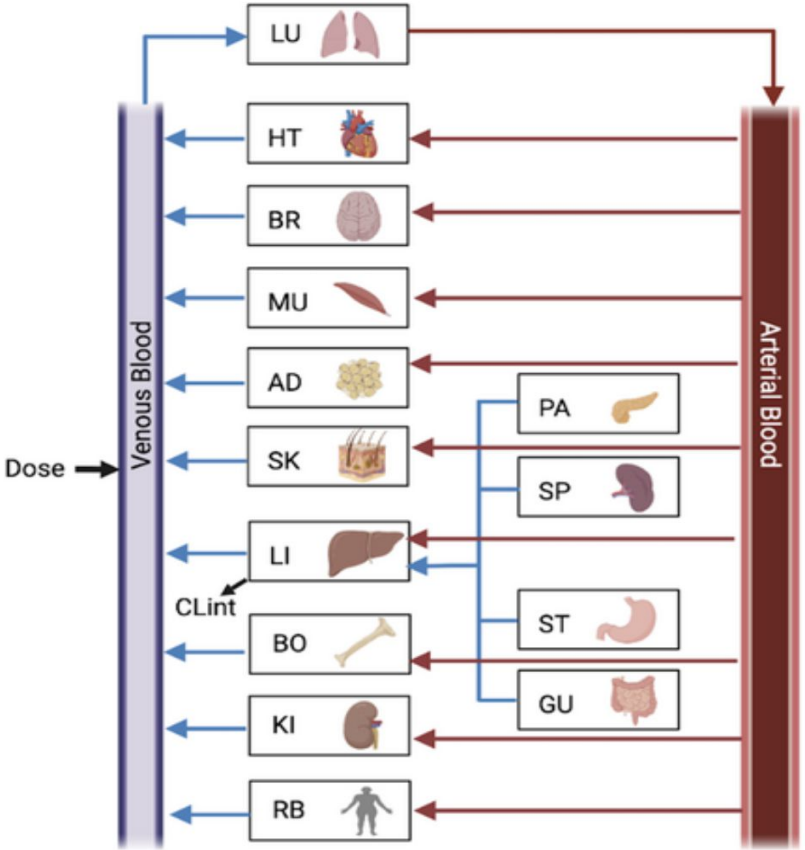
Bayesian PBPK modeling using R/Stan/Torsten and Julia/SciML/Turing.Jl

Ahmed Elmokadem, Yi Zhang, Timothy Knab, Eric Jordie, William R. Gillespie

First published: 20 January 2023 | https://doi.org/10.1002/psp4.12926

Case Study - Model Structure

Mavoglurant single
25 or 37.5 mg



Case Study: Statistical Model

Hierarchical model structure:

$$log(c_{ij}) \sim N(log(\hat{c}_{ij}), \sigma^2)$$

$$\hat{c}_{ij} = f_{PBPK}(t_{ij}, D_i, p_i)$$

$$p_i = [\theta_i, v_i]$$

$$\theta_i = [CLint_i, KbBR, KbMU, KbAD, KbBO, KbRB]$$

$$log(CLint_i) \sim N(log(\widehat{CLint}), \omega^2)$$

Priors:

$$\widehat{CLint} \sim lognormal(7.1, 0.25^2)$$

$$KbBR \sim lognormal(1.1, 0.25^2)$$

$$KbMU \sim lognormal(0.3, 0.25^2)$$

$$KbAD \sim lognormal(2, 0.25^2)$$

$$KbBO \sim lognormal(0.03, 0.25^2)$$

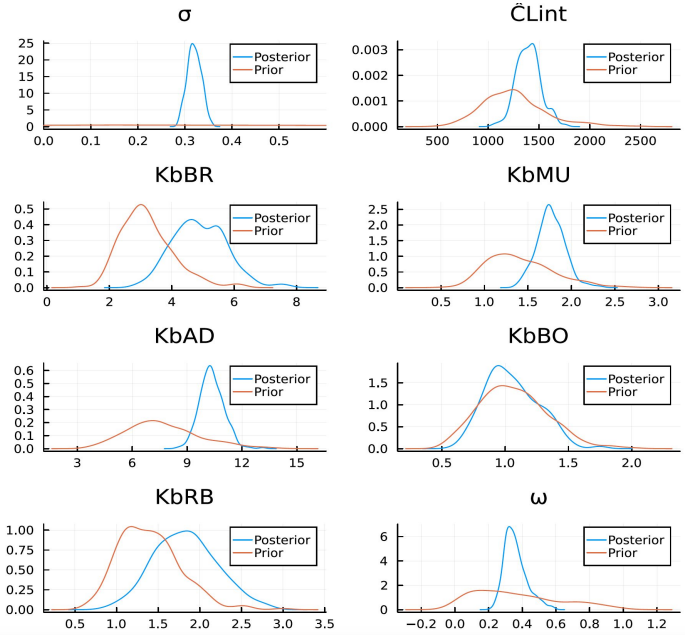
$$KbRB \sim lognormal(0.3, 0.25^2)$$

$$\omega \sim half - Cauchy(0, 0.5)$$

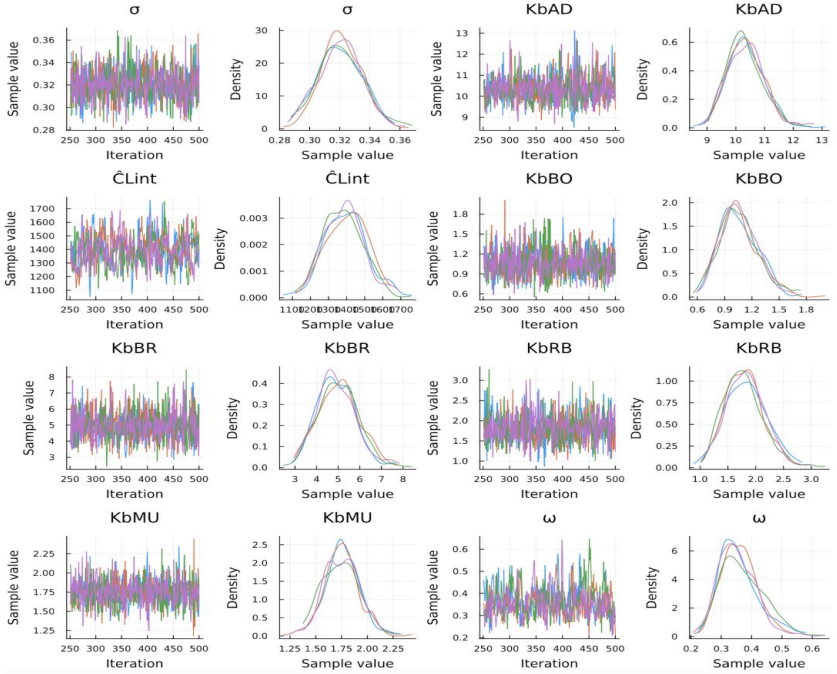
$$\sigma \sim half - Cauchy(0, 0.5)$$

Case Study: Diagnostics

Prior vs Posterior distributions



Trace and density plots



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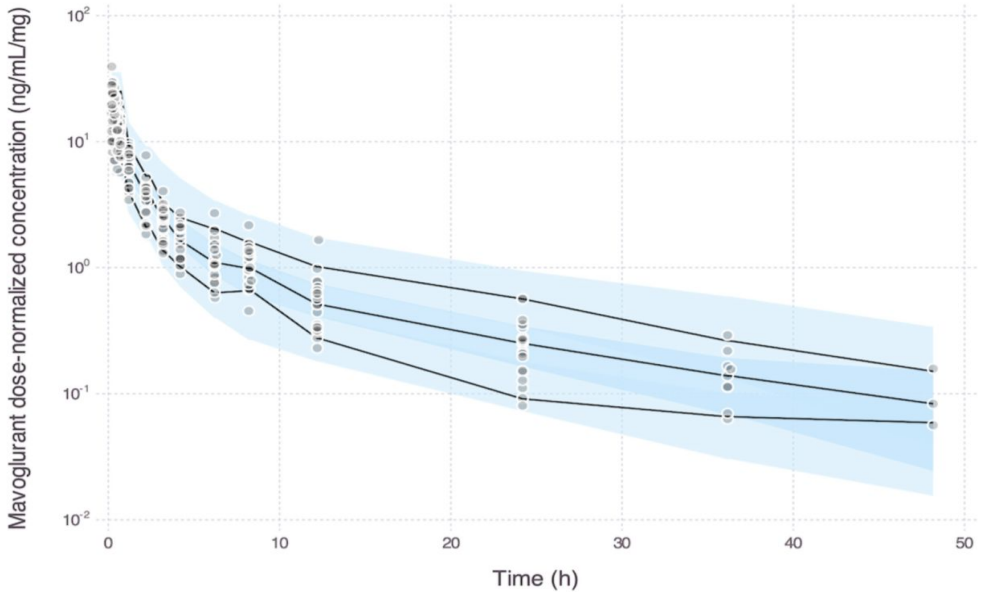
Case Study: Parameter Summary

Parameter estimates

Parameter	Mean (SD)	Median (90% CI)	$\hat{R}$	ESS-bulk	ESS-tail
$\hat{C}Lint$ (L/h)	1392 (113)	1390 (1216, 1585)	1.004	280	527
KbBR	4.97 (0.914)	4.9 (3.54, 6.54)	0.999	1382	718
KbMU	1.75 (0.171)	1.75 (1.49, 2.04)	1.009	1059	737
KbAD	10.3 (0.647)	10.3 (9.37, 11.46)	0.999	1056	773
KbBO	1.06 (0.214)	1.04 (0.74, 1.42)	0.999	1351	700
KbRB	1.8 (0.358)	1.8 (1.26, 2.43)	1	1315	876
ω	0.36 (0.066)	0.352 (0.27, 0.484)	1.002	268	352
σ	0.32 (0.015)	0.32 (0.297, 0.345)	1	1084	676

Case Study: Further Validation with PPC

Posterior predictive check



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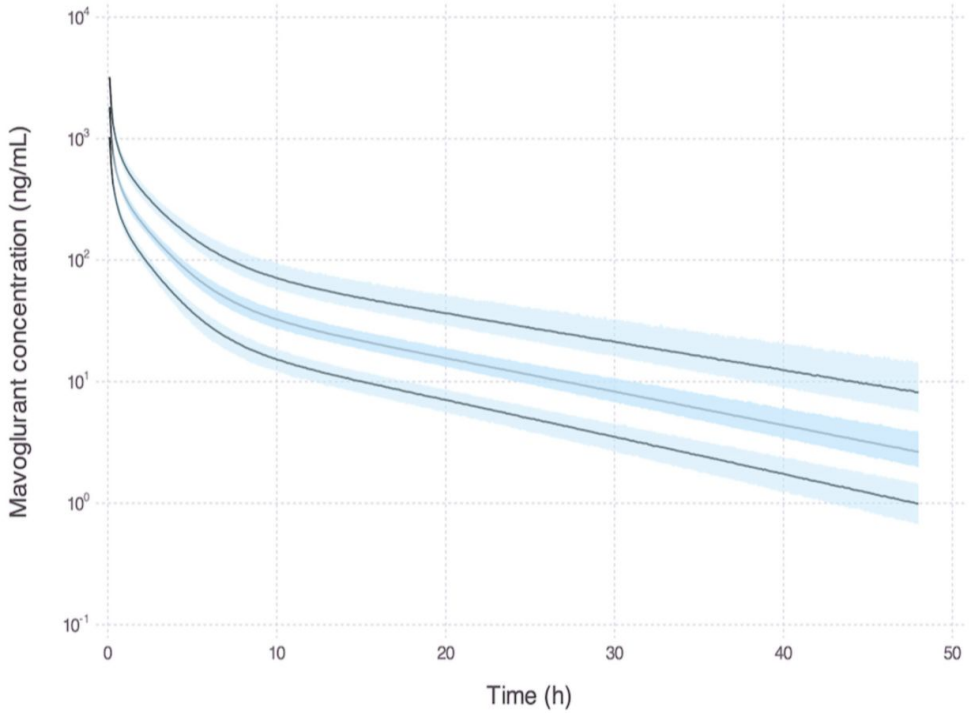
Case Study: Simulation

What if we dosed 50 mg?



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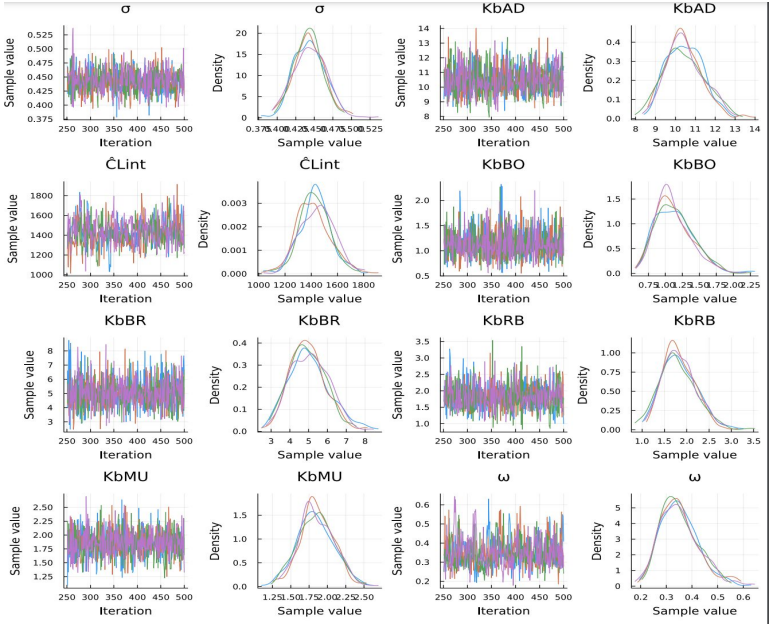
Case Study - Linear Exponential

- If the DE model is linear, it can be represented as: $y'(t) = Ky(t)$
- In this case, we can use a special solver `LinearExponential`, which is more efficient than using numerical solvers.

MCMC trace and density plots



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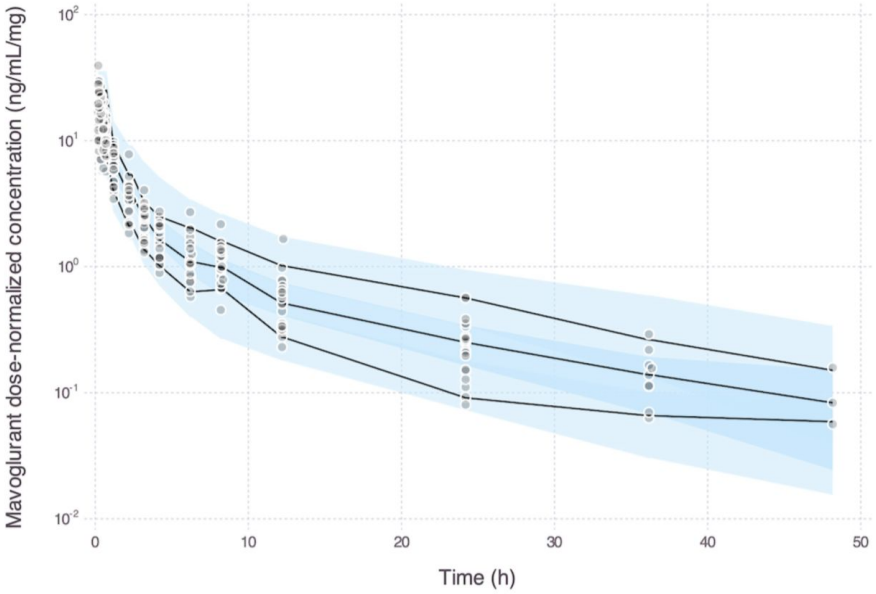
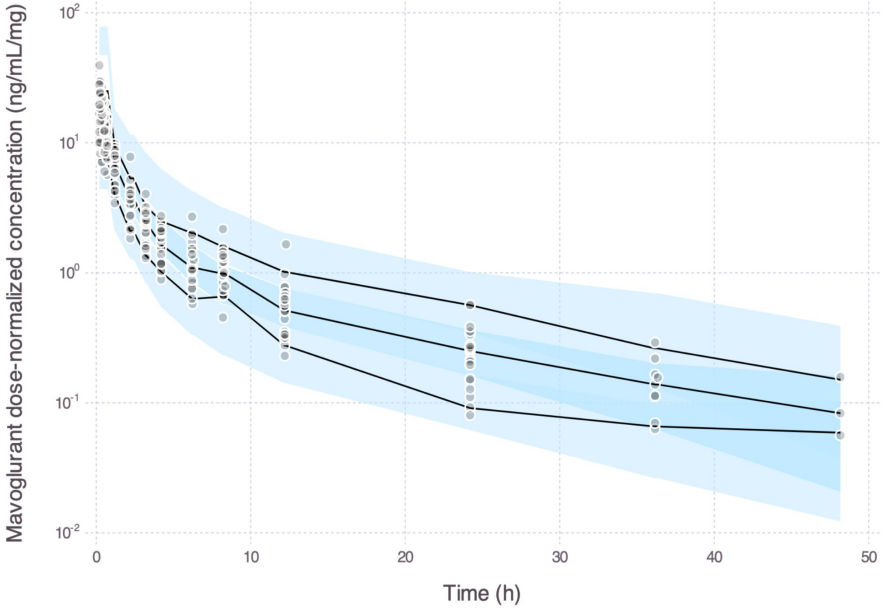
Case Study - Linear Exponential PPC

Numeric solver ~ 16 hours



Linear exponential ~ 4 hours



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Conclusions

- Bayesian PBPK combines the best of both worlds since it uses the mechanistic prior knowledge available to build PBPK models and updates it with data while quantifying the uncertainty through Bayesian inference.
- A framework was demonstrated that uses open-source Julia tools to successfully run Bayesian PBPK analysis.
- The composability of Julia tools allowed for the seamless integration of different functions in the proposed framework including sensitivity analysis, Bayesian inference, post-processing, running simulations, etc...
- Linear complex models can be defined using LinearExponential to be more efficient.
- The proposed framework can be generally applied to similar DE-based problems where prior knowledge might be significant.
- Check out the Github repository https://github.com/metrumresearchgroup/BayesPBPK-tutorial

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Metrum Research Group

- TSP group
  - Eric Jordie
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  - Katharina Wilkins
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  - Yuezhe Li
  - Jimena Davis
  - Ellen Swanson
- Matthew Riggs
- William R Gillespie
- Stacey Tannenbaum

Yi Zhang

Thank You

Backup

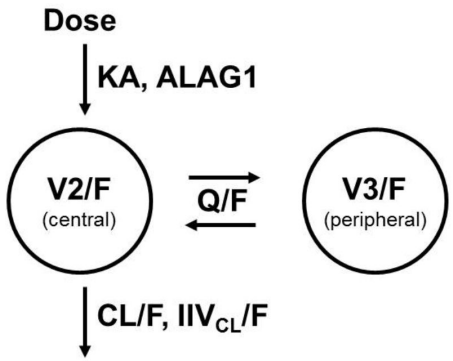
Literature on Bayesian PBPK

- Krauss et al. (2013) **Using Bayesian-PBPK modeling for assessment of inter-individual variability and subgroup stratification.**
- Krauss et al. (2015) **Bayesian Population Physiologically-Based Pharmacokinetic (PBPK) Approach for a Physiologically Realistic Characterization of Interindividual Variability in Clinically Relevant Populations.**

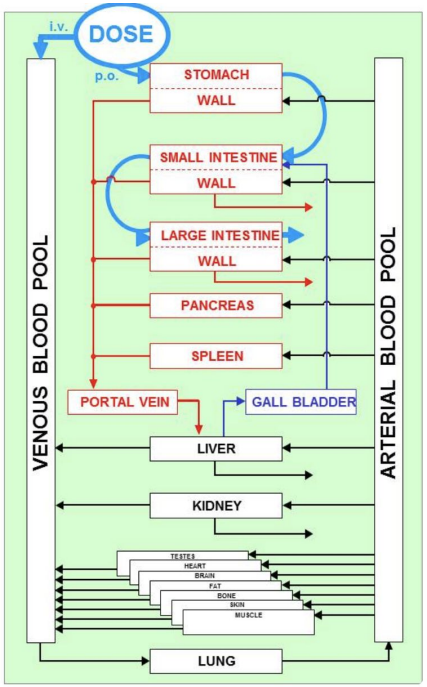
Introduction to PBPK Modeling - Why PBPK?

- Advantages of PBPK:
  - Bottom-up approach
  - *In vitro* to *in vivo* scaling
  - Special populations
  - Intra- and inter-species scaling
  - Monitor drug concentration at target site
  - Environmental toxicology
- Disadvantages of PBPK:
  - Complex
  - Computation time

A



B



https://docs.open-systems-pharmacology.org/mechanistic-modeling-of-pharmacokinetics-and-dynamics/modeling-concepts/modeling-concepts-pbpk-modeling-systems-biology

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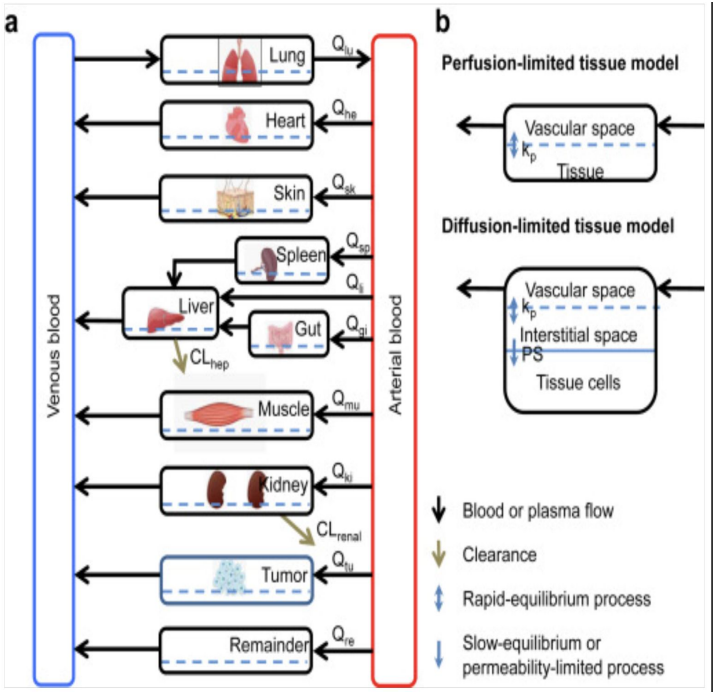
Introduction to PBPK Modeling - Structure and Types

- Physiologically based pharmacokinetic (PBPK) models are mechanistic mathematical models that characterize a drug's pharmacokinetics (absorption, distribution, metabolism, and excretion) in the body.
- They are multi-compartment models that use differential equations to describe the rate of change of the drug's concentration across different organs of the body.
- Types of PBPK models:
  - Flow/Perfusion-limited
  - Permeability/Diffusion-limited



Yuan et al. (2018)

Introduction to PBPK Modeling - Software and Resources

- Software landscape:
  - Commercial:
    - Simcyp
    - GastroPlus
    - Pumas
  - Open-source:
    - PK-Sim
    - mrgsolve
- Further resources:
  - Jones and Rowland-Yeo (2013): **Basic Concepts in Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development** 10.1038/psp.2013.41
  - Kuepfer et al. (2016): **Applied Concepts in PBPK Modeling: How to Build a PBPK/PD Model** 10.1002/psp4.12134
  - Elmokadem et al. (2019): **Quantitative Systems Pharmacology and Physiologically-Based Pharmacokinetic Modeling With mrgsolve: A Hands-On Tutorial** https://doi.org/10.1002/psp4.12467
  - Chigutsa et al. (2022): **A Quantitative Modeling and Simulation Framework to Support Candidate and Dose Selection of Anti-SARS-CoV-2 Monoclonal Antibodies to Advance Bamlanivimab Into a First-in-Human Clinical Trial** 10.1002/cpt.2459

Introduction to PBPK Modeling - continued

- Software landscape:
  - Commercial:
    - Simcyp https://www.certara.com/software/simcyp-pbpk/?utm_medium=ppc&utm_source=googleads&utm_content=simcyp&utm_campaign=productsimcyp&gclid=Cj0KCQjw8e-gBhD0ARIsAJiDsaV4hG_0n64-tTQUI5F67sQp1xfBRaJBoa37fodCEAxaotF1xtOLGOUaAuRbEALw_wcB&gclsrc=aw.ds
    - GastroPlus https://www.simulations-plus.com/software/gastroplus/?gclid=Cj0KCQjw8e-gBhD0ARIsAJiDsaVmOSJl63gfsTJPlzrmzeARd9YTxNK669HZhpCHf2A5V6dMWCK-BoQaAoULEALw_wcB
    - pumas https://pumas.ai/products/pumas/academia/
  - Open-source:
    - PK-Sim https://www.open-systems-pharmacology.org/
    - mrgsolve: https://mrgsolve.org/
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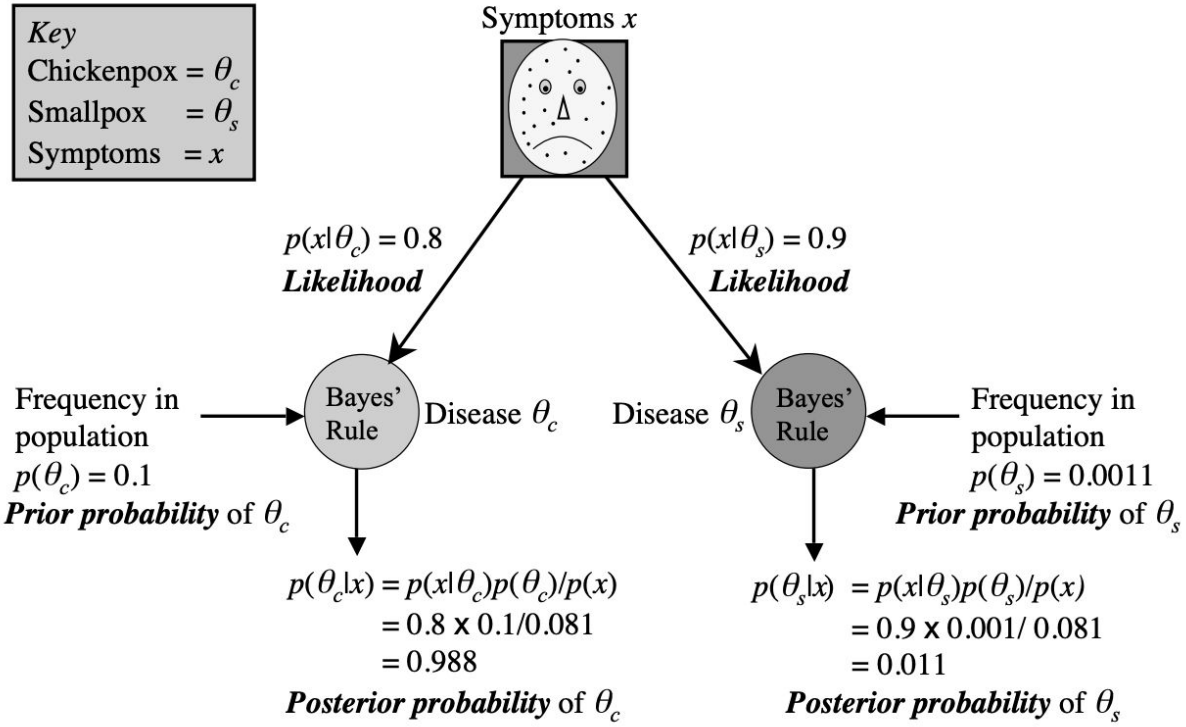
Case Study - Data

- Mavoglurant was a small molecule drug candidate for the treatment of fragile-X-syndrome that was discontinued in 2014 after disappointing trial results.
- Data:
  - PK data (mavoglurant plasma concentration-time data) that were used for this case study were part of study A2121 that characterized the PK of mavoglurant in healthy volunteers.
  - The PK data for 20 subjects were picked for this demonstration.
  - These subjects were administered single 25 or 37.5 mg IV doses of mavoglurant that were infused with rates ranging from 75 to 225 mg/h.
  - The dataset included individual subject weights, which were used to scale the individual physiological parameters in the PBPK model. Eg:

$$CO = aWT^b$$

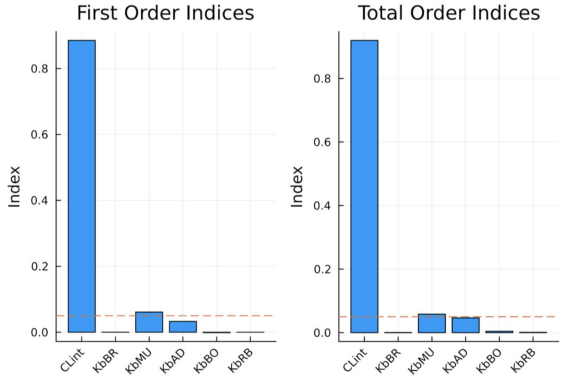
Bayesian Inference - Intuition



Stone, James V (2013)

Case Study: Results

Sobol global sensitivity



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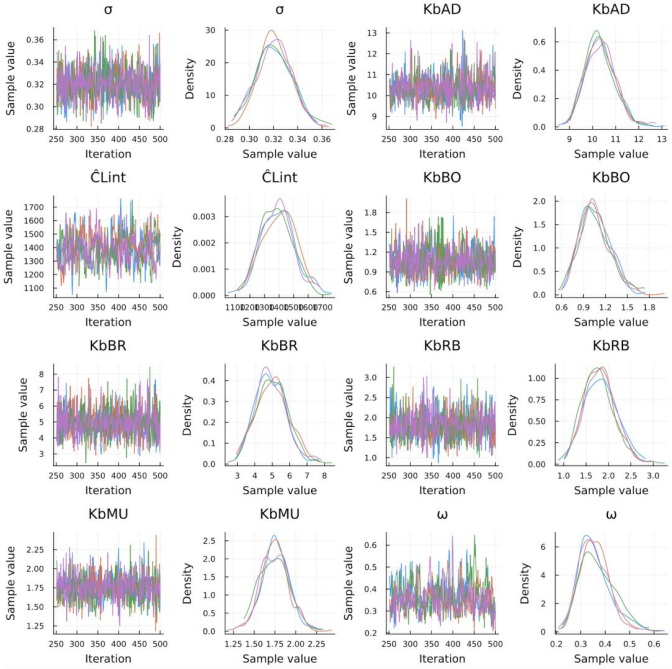
SD = standard deviation; CI = credible interval; $\hat{R}$ = Gelma-Rubin statistic; ESS = effective sample size; $\hat{C}Lint$ = population intrinsic clearance; KbBR, KbMU, KbAD, KbBO, and KbRB are the brain, muscle, adipose, bone, and rest of body tissue:plasma partition coefficients, respectively; ω = standard deviation of $\hat{C}Lint$ intersubject

MCMC trace and density plots



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