Fast simulation of pharmacokinetics

and some words about modeling

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Friday Seminar Oct 7, 2022

About me

Background:

- MSc Engineering Physics, LTH, 2019
- Project assistant, Automatic Control, Sep 2019 - Apr 2020

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Two research directions:

- Heart transplantation project at Igelösa - to increase the number of transplanted hearts. With Kristian and Harry.
- Pharmacokinetic-pharmacodynamic (PKPD) modeling and control. With Kristian, Jesper and some others (Fredrik Bagge, Martin Morin. . .)

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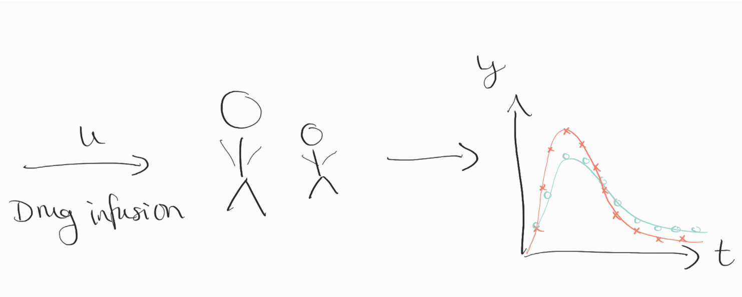
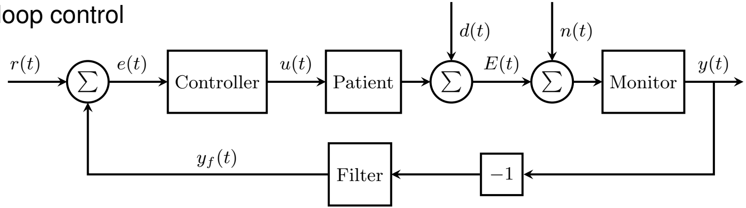
- Modeling
- Fast simulation of pharmacokinetics
- Future work - symbolic regression networks for population modeling

Motivation - inter-patient variability



Inter-patient variability - how do we approach this?

- Closed-loop control



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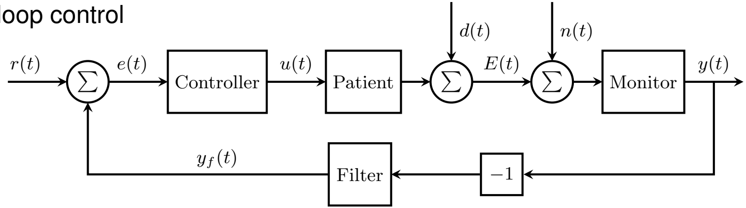
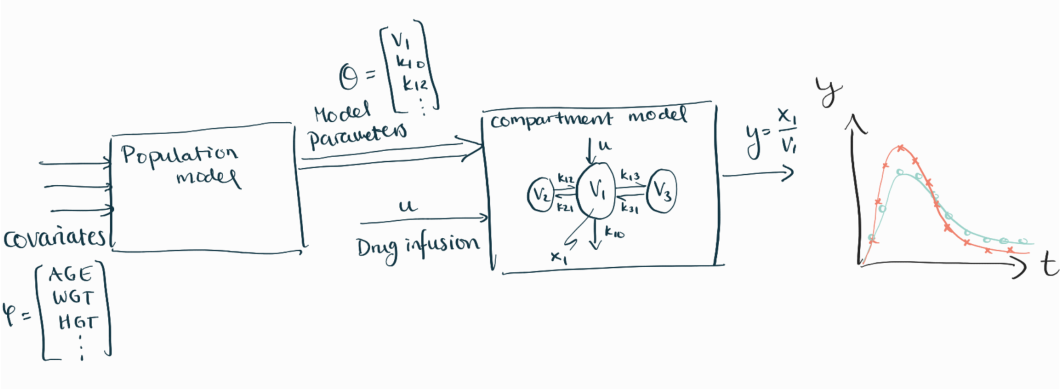


- Open-loop. Population modeling, based on measurements from patients of different age, weight, gender etc.

Modeling



Θ = [V1, k10, k12, ⋮]
Model parameters
Population model
covariates
φ = [AGE, WGT, HGT, ⋮]
u
Drug infusion
compartment model
u
V2
k12
k21
V1
k13
k31
V3
k10
x1
y = x1/V1
y
t

Population modeling

Examples from a population model:

$$V_2 = \theta_2 \frac{\mathsf{WGT}}{70} \exp(\theta_{10}(\mathsf{AGE} - 35)) \exp(\eta_2)$$

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$$Q_2 = \theta_5 V_2^{0.75} \left(1 + \theta_{16} \left(1 - \frac{\mathsf{AGE}}{\mathsf{AGE} + \theta_{14}}\right)\right) \exp(\eta_5)$$

Many simulations are required to identify structure and parameters θ.

Fast simulation of pharmacokinetics

Why are the current simulation methods not good enough?
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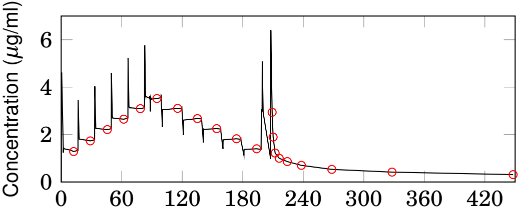
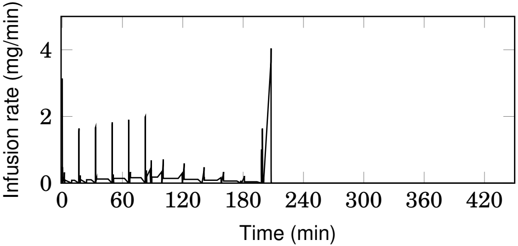
(lsim, DifferentialEquations, direct computation with $x_{k+1} = \Phi x_k + \Gamma u_k$)
Input data is a combination of impulses (boluses) and steps (constant infusions).



(a) Simulation output, blood plasma concentration



(b) Input, infusion rate

Fast simulation of pharmacokinetics

Transfer function for the n-compartment model

$$\frac{Y(s)}{U(s)} = \frac{1}{V_1} \frac{(s-p_1)(s-p_2)...(s-p_{n-1})}{(s-\lambda_1)(s-\lambda_2)...(s-\lambda_n)}$$

Fast simulation of pharmacokinetics

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Partial fraction decomposition gives us

$$\frac{Y(s)}{U(s)} = \frac{1}{V_1} \sum_{j=1}^{n} \frac{r_j}{s-\lambda_j}$$

All parameters (p,λ,r) can be determined explicitly for low-order models (at least $n \leq 3$).

Fast simulation of pharmacokinetics

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$$\frac{1}{s-\lambda_j}$$

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Zero-order hold with sampling period h_k results in

$$z_{k+1} = \varphi_j z_k + \gamma_j u_k,$$

where

$$\varphi_j = e^{\lambda_j h_k}$$
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and the concentration becomes

$$y_k = \frac{1}{V_1} R^T \boldsymbol{z_k}$$

Now, we can simulate n models of order 1 instead of simulate a model of order n.

Preliminary results

Table: Wall-clock time for simulation of a data set with 1033 patients. The simulations has been performed in Matlab and Julia, using different simulation methods. Memory allocation count is not accessible for the Matlab simulation.

Software	Method	Time (ms)	Allocations
Matlab	`lsim`	1822	-
Julia	$x_{k+1} = \Phi_k x_k + \Gamma_k u_k$	548	$2.03 \cdot 10^6$
Julia	DifferentialEquations	230^*	$2.79 \cdot 10^{7*}$
Julia	Proposed simulation	1.63	0

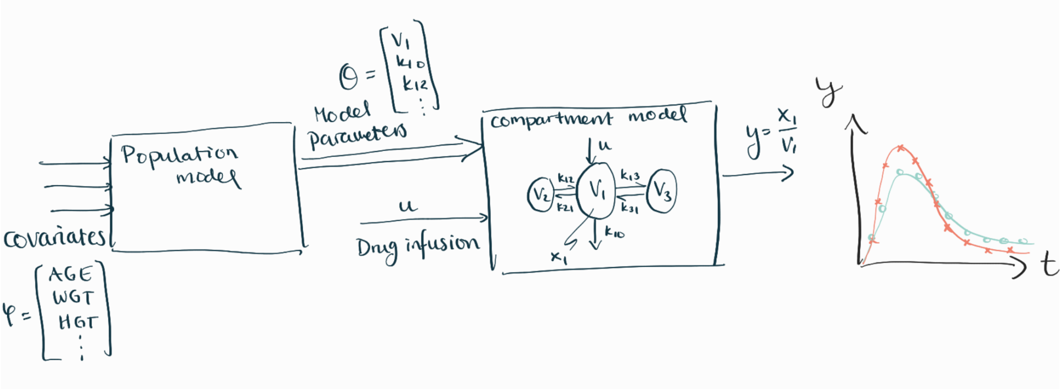
* Preliminary results

Fast simulation of pharmacokinetics

The simulator can be found in the Julia package

`https://github.com/wahlquisty/FastPKSim.jl` (thanks to the Julia course)

Future work - symbolic regression networks for population modeling



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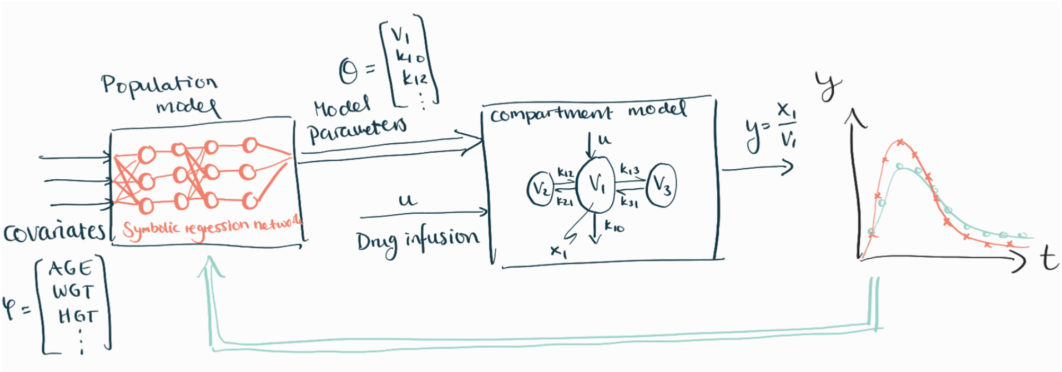

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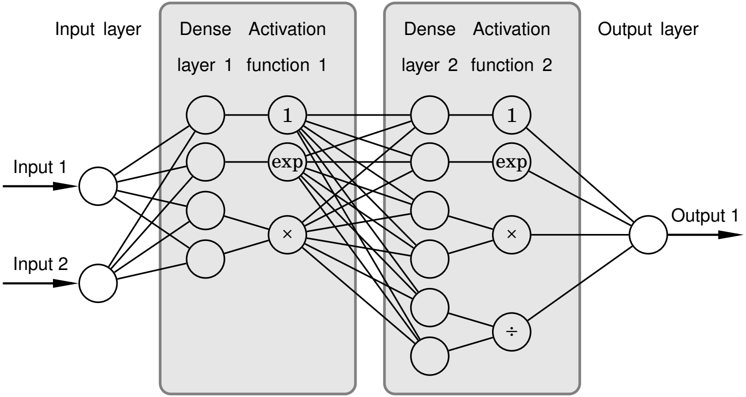
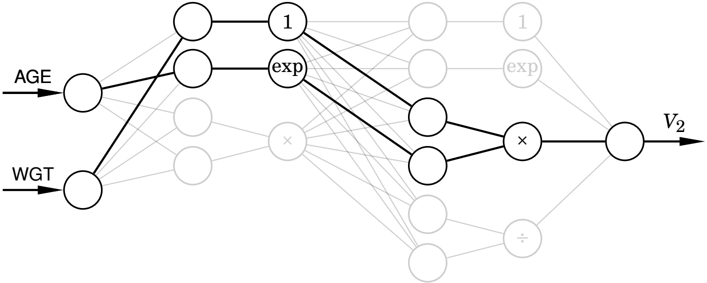


Figure: Nominal expression tree with two hidden layers, each marked by a gray box.

Example, find V_2



$$V_2 = 0.624 WGT \exp(-0.0155 AGE)$$