Case Study: Parameter Estimation of an NLME-QSP Model

David Müller-Widmann[1], Andreas Noack[1]

1. Pumas-AI Inc. Dover, DE 19901

INTRODUCTION

Typically, quantitative systems pharmacology (QSP) models and nonlinear mixed effects (NLME) models of pharmokinetics (PK) and pharmacodynamics (PD) are used at different stages of the drug development process.

In this case study, we combine these two modeling approaches in an NLME-based PK/PD model whose dynamics are governed by the QSP model ("NLME-QSP model").

OBJECTIVES

Analyze the feasibility of parameter estimation of an NLME-QSP model using first-order conditional estimation (FOCE).

METHODS

We consider the following study design (based on [3]):

- Daily subcutaneous injections of teriparatide 20 µg
- PTH (parathyroid hormone) [pg/mL] measured in sampling windows of 0 – 30 min, 30 min – 1 hr, 1 – 2 hr, 2 – 3 hr and 3 – 4 hr post-dose at 1 month of treatment
- Serum calcium [mg/dL] measured at time of first dose and at 4 – 6 hr post-dose at 1 month of treatment

The calcium and PTH response to teriparatide is modeled with the QSP model of integrated calcium homeostasis and bone remodeling by Peterson & Riggs [2] (http://identifiers.org/biomodels.db/BIOMD0000000613). As in [2], the PK of teriparatide is modeled with a depot compartment with first-order absorption into the compartment of circulating PTH.

Parameters of the QSP model relevant for inference under the considered study design are identified with a two-stage sensitivity analysis of the PTH and calcium values at the average sampling times:

1. Local sensitivity analysis with respect to all QSP model parameters at their literature values
2. Global sensitivity analysis with respect to the 10 most sensitive QSP model parameters using Sobol's method

The most sensitive PK and PD parameters are integrated into the NLME-QSP model; all other parameters of the QSP model are fixed to their literature values. Additionally, the NLME model consists of

- a power model with fixed exponent 0.75 to describe the relation of the PK parameter on normalized body weight,
- log-normally distributed inter-individual variability of the PK parameter,
- and proportional Gaussian error models of the measured concentrations of PTH and serum calcium.

A population of 10 subjects is simulated based on the distribution of body weight reported in [3] and by drawing sampling times uniformly at random from the specified sampling windows. Measurements of PTH and serum calcium are simulated for each subject by setting the population values of the PK and PD parameters to their literature values and assuming a CV% of 10 for IIV and RUV.

Parameter inference with the simulated dataset is performed using FOCE, starting from perturbed PK and PD population parameter values and increased CV%. The log-likelihood of the fitted parameters is compared to the log-likelihood of the data-generating parameters and the perturbed parameters.

All analyses were performed on the JuliaHub computing platform using the Julia programming language and Pumas (version 2.7.0).

CONTACT

www.pumas.ai/resources

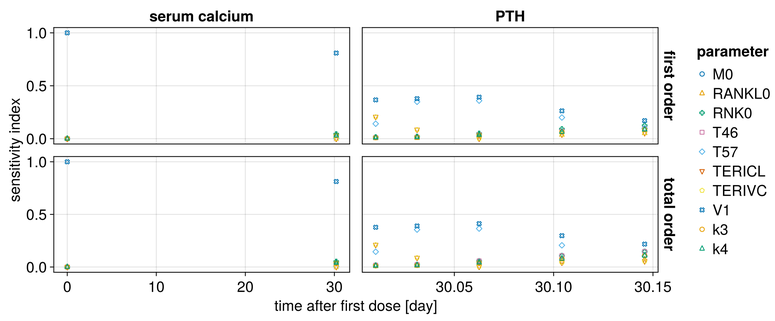
David Müller-Widmann d.widmann@pumas.ai

RESULTS: SENSITIVITY ANALYSIS

Table 1: The 10 most sensitive QSP model parameters in terms of 2-norm of the relative sensitivities (normalized with respect to parameter and output values).

Parameter	Description	Norm of relative sensitivities
V1	V_{vasc} (vasculature volume)	2.4149
T57	degradation rate constant of PTH	1.8641
T46	$\varphi_{5\text{-}u}$	1.6238
RNK0	initial value RANK	1.4091
M0	initial value RANK-RANKL	1.2639
k3	$k_{21\text{-}24}$ (association rate constant of RANK and RANKL)	1.2639
k4	$k_{24\text{-}21}$ (dissociation rate constant of RANK-RANKL)	1.2636
TERICL	clearance of teriparatide	1.2126
TERIVC	volume of teriparatide	1.2126
RANKL0	initial value RANKL	1.0160

Figure 1: The first and total order sensitivity indices of the 10 most sensitive QSP model parameters.



RESULTS: PARAMETER ESTIMATION

Figure 2: Pumas implementation of the NLME-QSP model.

```
@model begin
  @options begin
    symbolic_jacobian = true
  end

  @param begin
    # PK
    θTERICL ∈ RealDomain(; lower = 0.0)
    ω ∈ RealDomain(; lower = 0.0)

    # PD
    V1 ∈ RealDomain(; lower = 0.0)

    # Error models
    σprop_PTH ∈ RealDomain(; lower = 0.0)
    σprop_Ca ∈ RealDomain(; lower = 0.0)
  end

  @covariates weight_kg

  @random begin
    η ~ Normal(0.0, ω)
  end

  @pre begin
    TERICL = θTERICL * (weight_kg/70)^0.75 * exp(η)
  end

  @dynamics BoneQSP

  @derived begin
    # PTH [pg/mL]
    PTH_pgmL := @. PTH / V1 * 9.4
    dvPTH ~ @. Normal(PTH_pgmL, σprop_PTH * abs(PTH_pgmL))

    # calcium [mg/dL]
    Ca_mgdL := @. P / V1 * 4
    dvCa ~ @. Normal(Ca_mgdL, σprop_Ca * abs(Ca_mgdL))
  end
end
```

Table 2: Parameter values.

Parameter	Data generation	Initial estimate	Estimated
θTERICL	94.3	103.73	98.42
ω	0.1	0.2	0.15
V1	14.0	12.6	14.2
σprop_PTH	0.1	0.5	0.09
σprop_Ca	0.1	0.5	0.11

Table 3: Log-likelihood values.

Parameter	Log-likelihood
Data generation	-234.07
Initial estimate	-319.15
Estimated	-231.88

CONCLUSIONS

- NLME-based PK models and QSP models can be combined in an NLME-QSP model that is amenable to successful parameter estimation with Pumas.
- Many parameter configurations of the NLME-QSP model gave rise to complex ("stiff") dynamics on largely different timescales, which required algorithms specialized for stiff differential equations for sufficiently accurate and efficient simulation.
- Exposing too many parameters of the QSP model in the NLME-QSP model can lead to identifiability problems and increases the computational cost.
- Symbolic calculation of the Jacobian matrix of the QSP model improved performance and stability of the estimation.
- Parameter estimation failed when solving the inner optimization problem of FOCE too loosely.

REFERENCES

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[3] Satterwhite, J., Heathman, M., Miller, P. D., Marín, F., Glass, E. V., & Dobnig, H. (2010). Pharmacokinetics of Teriparatide (rhPTH[1–34]) and Calcium Pharmacodynamics in Postmenopausal Women with Osteoporosis. Calcified Tissue International, 87(6), 485–492. https://doi.org/10.1007/s00223-010-9424-6