Modeling multi-center rare disease data: application to congenital hypothyroidism in newborns and infants

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Introduction and Objectives

Introduction

Data analysis and mathematical modeling of retrospectively collected multi-center data of a rare disease in pediatrics is challenging because laboratory data can stem from several decades measured with different assays resulting in diverse reference ranges. We present retrospective pharmacometrics (PMX) based data analysis and modeling of congenital hypothyroidism (CH) in newborns and infants in order to personalize dosing in this pediatric patient population as suboptimal treatment of CH during the first two years of life is associated with reduced IQ between 10-14 years.

Objectives

- Perform retrospective data analysis of multi-center data of CH
- Introduce scale/location-scale normalizing method for multi-assay data
- Develop PMX model for free thyroxine (FT4) concentration and levothyroxine (LT4) substitution treatment based on normalized FT4 measurements

Methods

Available data

- Based on inclusion and exclusion criteria, data from n = 61 pediatric patients (female 70%) up to approximately 2 years of age were available.
- FT4 and thyroid-stimulating hormone (TSH) measurements were performed between 01/1990 and 08/2018 in four Swiss pediatric centers
- A total of 505 FT4 measurements were available, on average 8 per patient

Normalizing method

- 34 different post natal age (PNA-) and assay-dependent laboratory reference ranges $[r_{low}, r_{up}]$ were identified for the 505 measurements.
- Distribution of our FT4 measurements changes during treatment from a left-skewed distribution towards approximately Gaussian distribution from threshold t_s onward, since successfully treated patients have FT4 values in the healthy target reference range.
- A time-dependent normalizing method is developed based on PNA-dependent target reference ranges $[r_{low}^{Std}, r_{up}^{Std}]$ [2].
- This normalizing method combines a scale formula [3] with a location-scale formula [1], i.e. x_{norm} is calculated from performed FT4 measurement x_{meas} by

$$x_{norm} = \begin{cases} \frac{t}{t_s} \cdot \left((x_{meas} - r_{low}) \cdot \frac{r_{up}^{Std} - r_{low}^{Std}}{r_{up} - r_{low}} + r_{low}^{Std} \right) + \left(1 - \frac{t}{t_s}\right) \cdot x_{meas} \cdot \frac{r_{up}^{Std}}{r_{up}} & for\ t \leq t_s \\ (x_{meas} - r_{low}) \cdot \frac{r_{up}^{Std} - r_{low}^{Std}}{r_{up} - r_{low}} + r_{low}^{Std} & for\ t > t_s \end{cases}$$

PMX model for FT4 concentration and LT4 treatment

- Absorption compartment A_B with exogenous LT4 treatment:

$$\frac{d}{dt} A_B = In(t_j, dose_j, F) - k_a \cdot A_B \qquad A_B(0) = 0,$$

with absorption rate k_a 1/day

- One-compartment PK model with constant endogenous thyroxine (T4) production rate k_{endo} nmol/day and absorption compartment A_B:

$$\frac{d}{dt} A_C = k_a \cdot A_B + k_{endo} - k_{el} \cdot A_C \qquad A_C(0) = \frac{k_{endo}}{k_{el}},$$

with elimination rate k_{el} 1/day

- Assuming FT4 concentration corresponds to 0.03% of T4:

$$C_{FT4} = 0.3 \cdot \frac{A_C}{V(W)}, \qquad (1)$$

where volume of distribution V l is proportional to (non-linear interpolated) current body weight $W(t)$ kg/day, i.e.
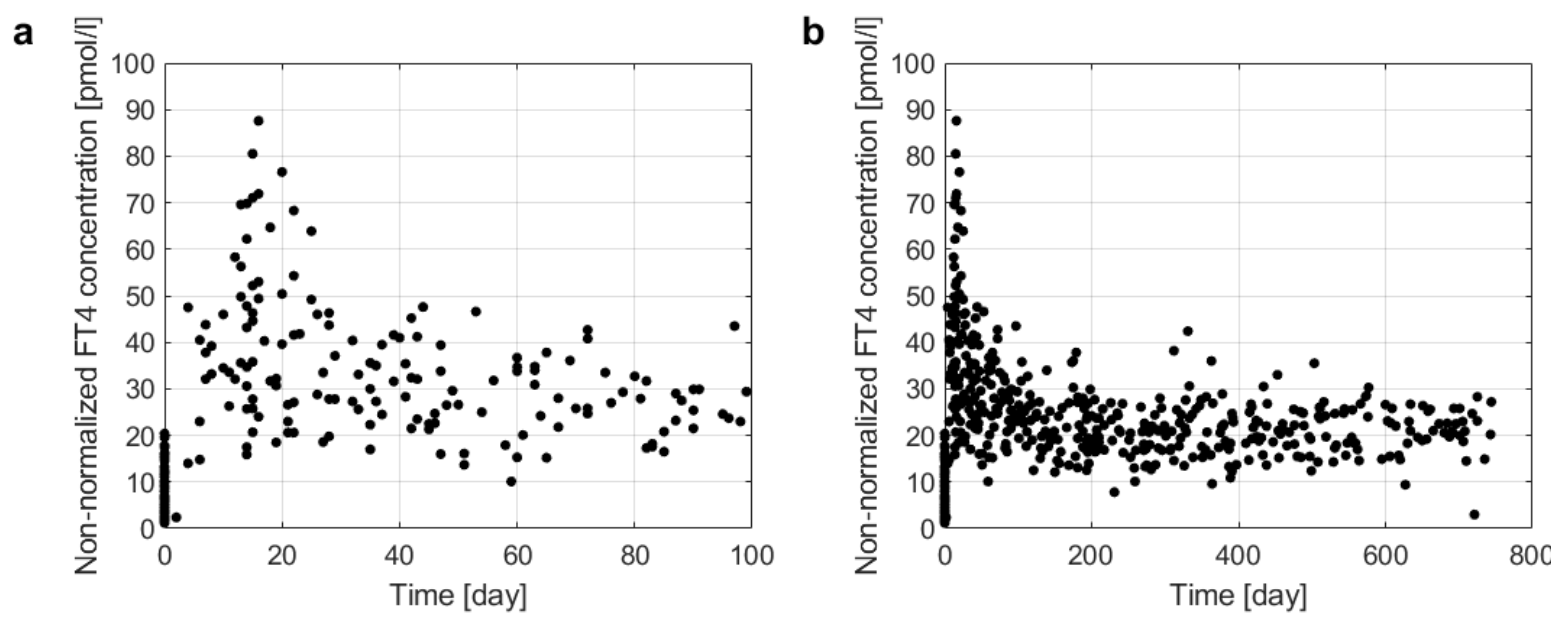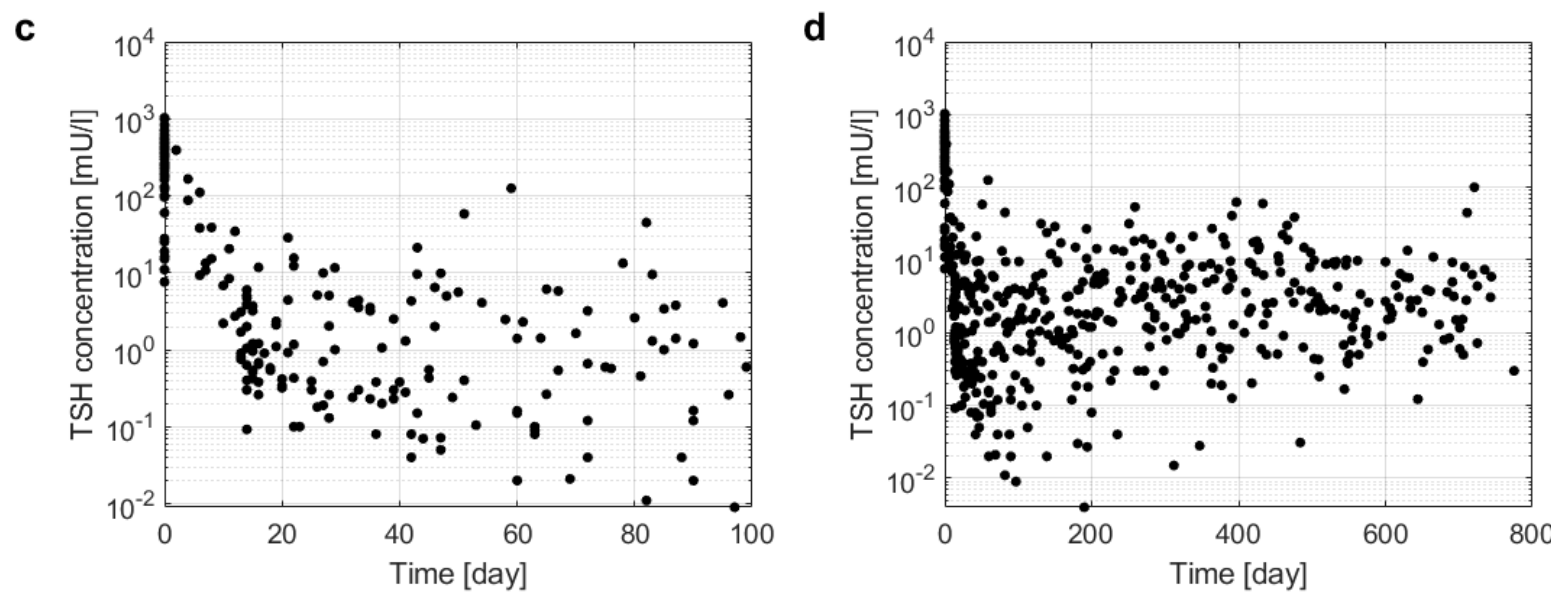
$$V(W) = f_V \cdot W(t).$$

Results

Data analysis of non-normalized measurements

- At start of treatment (at baseline): Median [IQR]
PNA 7 [6, 9] day, weight 3.3 [2.9, 3.8] kg, FT4 7.0 [3.4,12.3] pmol/l, TSH 266.8 [145.8, 429.4] mU/l
- At last available follow-up with FT4 measurement:
PNA 602 [362, 708] day, weight 11.3 [9.4, 12.7] kg, FT4 21.0 [18.4,25.6] pmol/l, TSH 2.2 [0.9, 4.7] mU/l

FT4 measurements (a) & (b)

TSH measurements (c) & (d)

Comparison of non-normalized and normalized measurements

- Normalized FT4 values slightly but not significantly lower than non-normalized FT4 measurements, thus they can be treated as if they were obtained from a single laboratory

Covariate selection and testing

- Body weight over time was already included in PMX model, Eq (1)
- PNA at baseline had only weak effect on k_{endo} and was not included
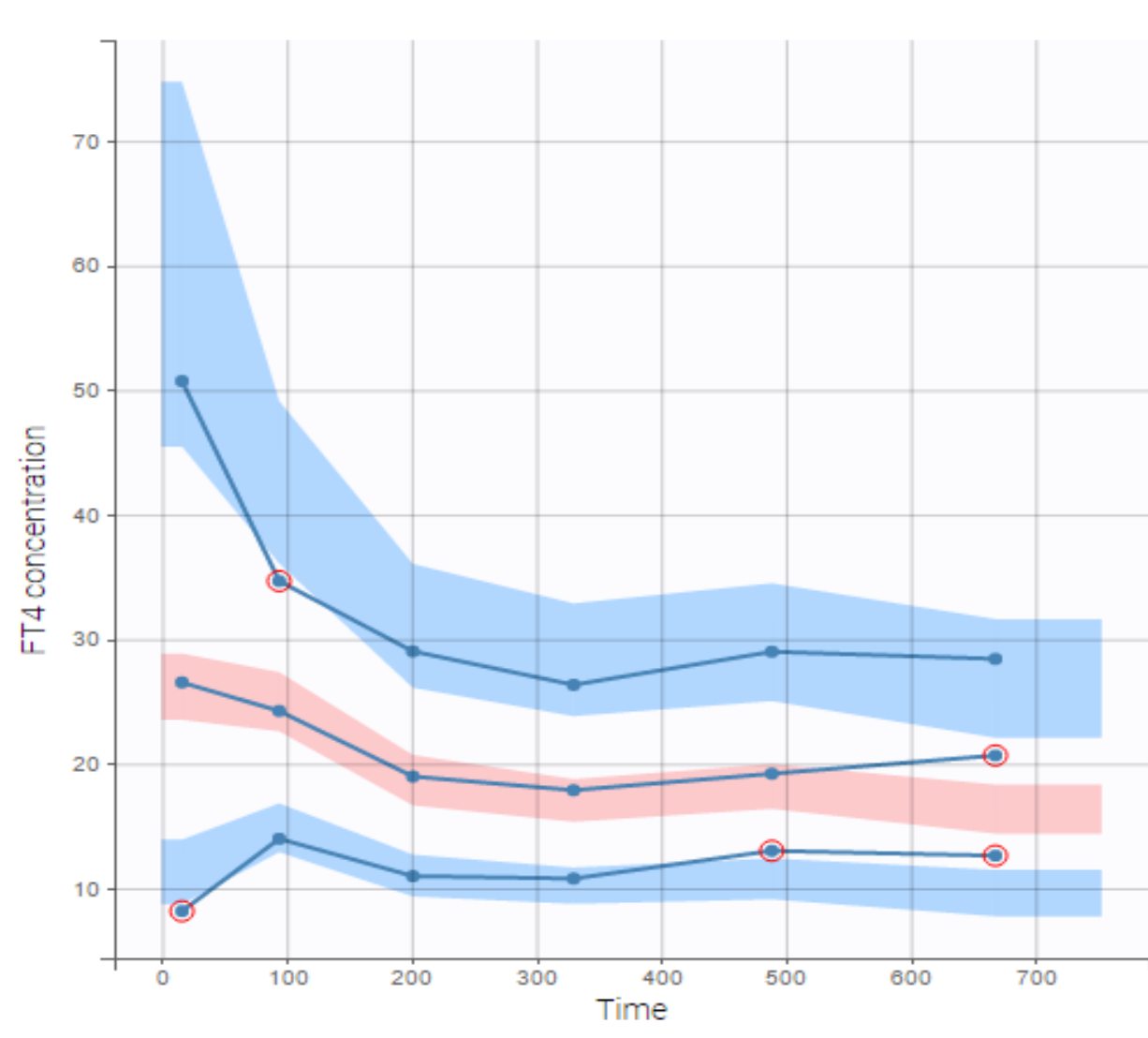- No obvious TSH feedback effect on k_{endo}

Parameter estimation based on normalized FT4 values

- Bioavailability F = 0.6, absorption rate $k_a = 20$ 1/day, elimination rate $k_{el} = 0.1$ 1/day fixed, no inter-individual variability
- Population estimates (r.s.e): k_{endo}= 3.22 (15) nmol/day, f_V = 0.573 (3.4) l/kg

Individual plots
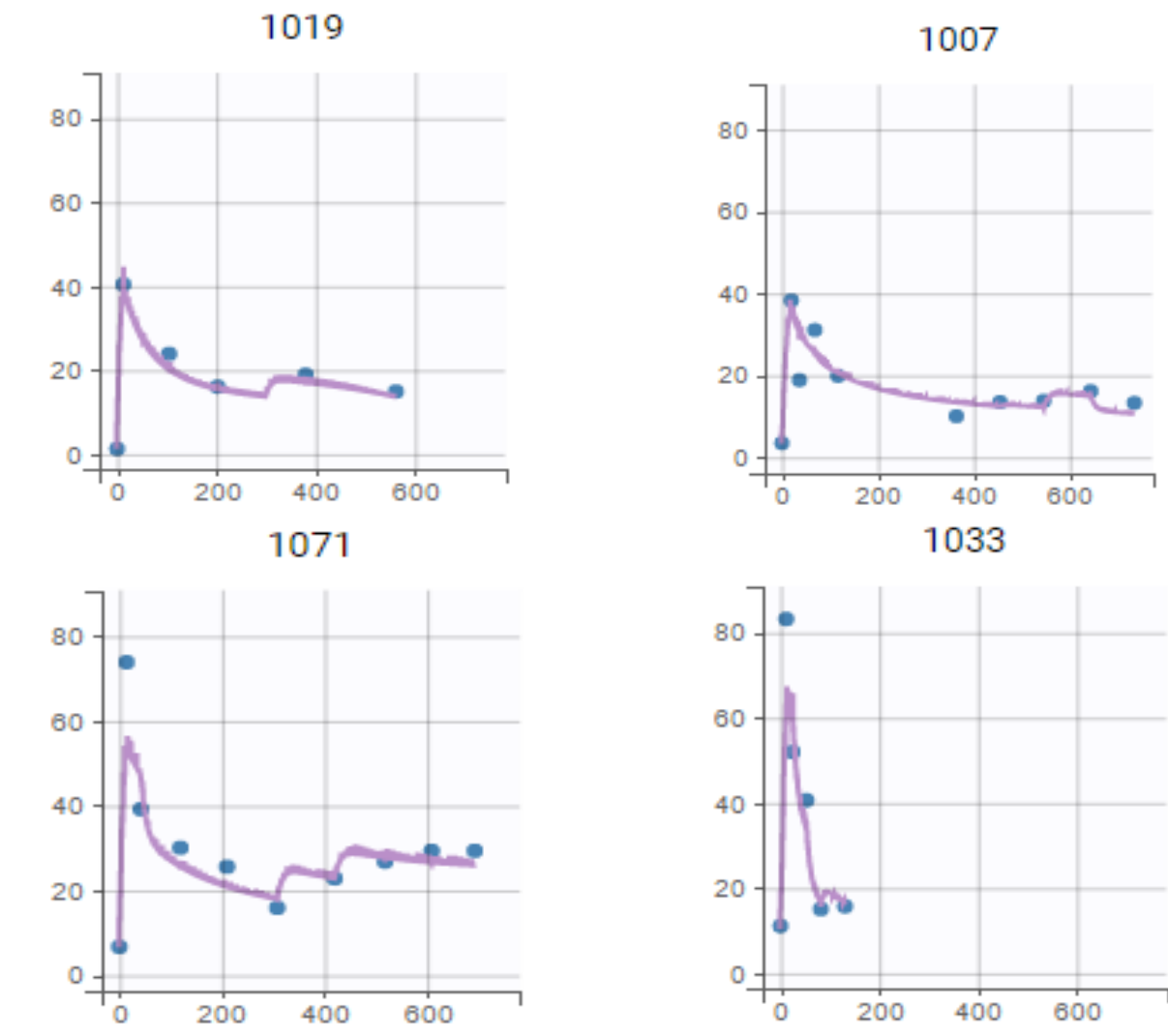
Visual predictive check

Conclusions

- A time-dependent scale/location-scale normalizing formula for measurements derived from distributions that change from a left-skewed towards approximately Gaussian distribution is introduced.
- A practical and clinically useful PMX model that characterizes FT4 concentration during LT4 treatment in neonates and infants with CH is developed.
- This retrospective PMX analysis paves the way for successful designing and planning of a prospective clinical study to evaluate the model.
- PMX based modeling and simulation can be leveraged to personalize dosing with the goal to further enhance longer-term outcome in pediatric patients with CH or other rare diseases.

References

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