Nonlinear Mixed Effects Modeling

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Introduction

Application of a mathematical model to longitudinal data requires that it is placed in a framework to acknowledge intra-subject variation

- measurement/assay errors
- model misspecification/numerical approximation

Application of a mathematical model to data from multiple subjects requires that it is placed in a framework that not only recognizes within-subject variation, as above, but also inter-subject variation

- variation in dynamic parameters across the population (heterogeneity of subjects within the population)

An Example: Logistic Equation

Our test model is the logistic equation

$$\frac{dP}{dt} = rP\left(1 - \frac{P}{K}\right)$$

The logistic equation (Verhulst model [1847]) is used to model population growth

For our test case, data was generated using

$$P(0) = 2, \quad t = 0, 1, 2, ..., 10 \quad v_k \sim N(0, 0.1)$$

To create variability, 100 profiles were created with different parameters having a normal distribution with mean and covariance

$$\mu = \begin{pmatrix} r \\ K \end{pmatrix} = \begin{pmatrix} 0.725 \\ 20 \end{pmatrix} \quad \Omega = \begin{pmatrix} 0.05 & 0 \\ 0 & 0.2 \end{pmatrix}$$

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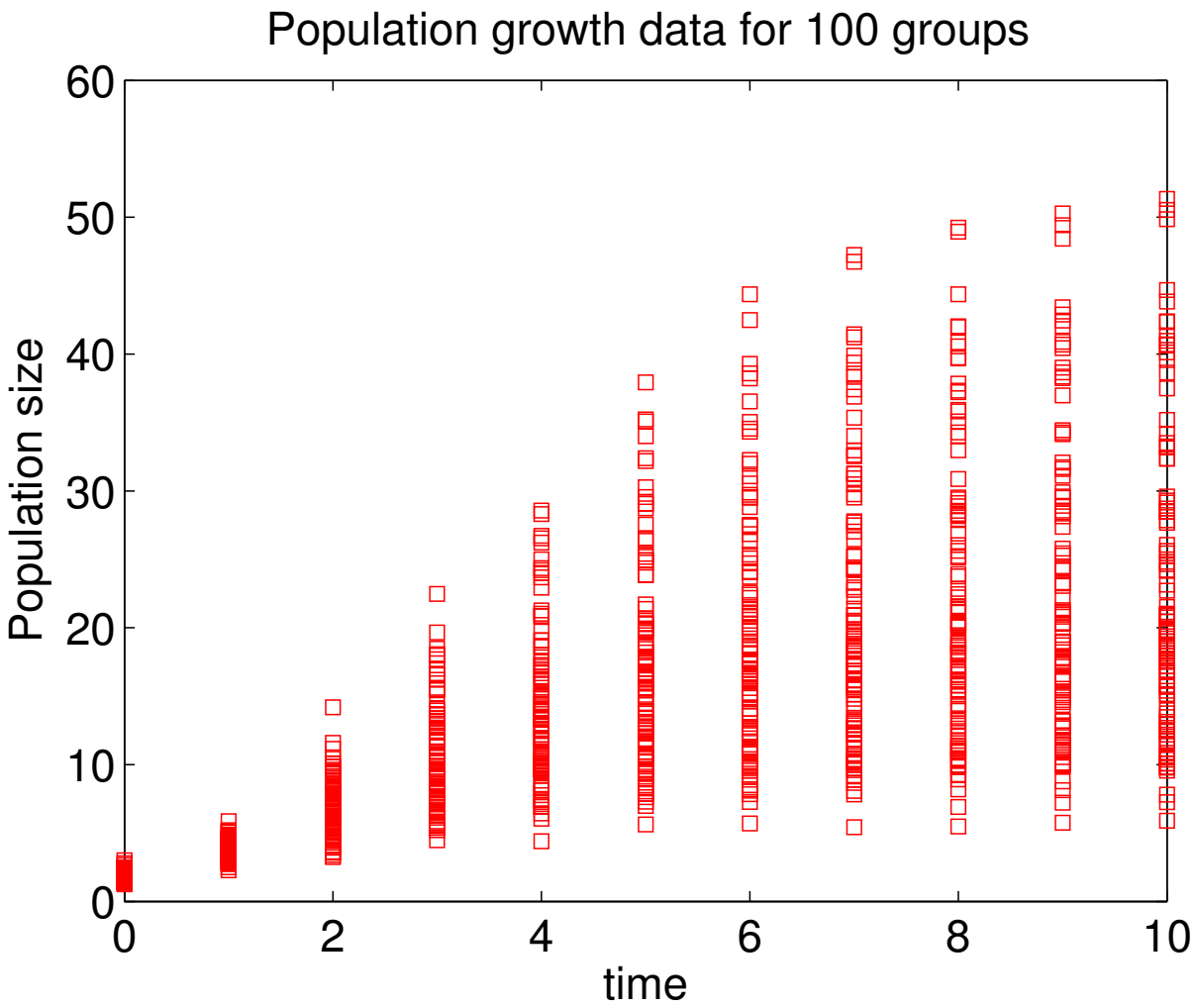
Data

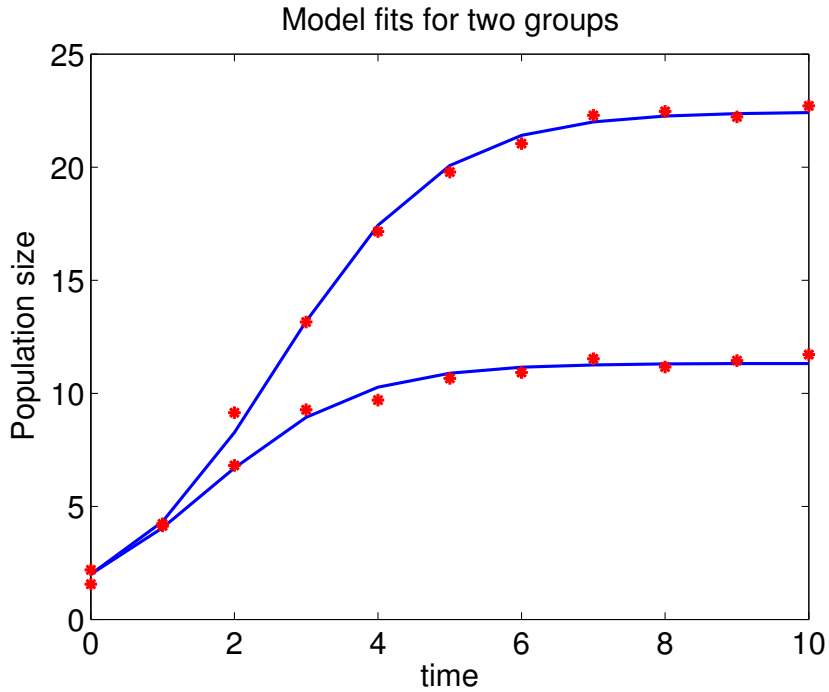

Population growth data for 100 groups
Population size
time
0
10
20
30
40
50
60
0
2
4
6
8
10

Two Stage Method

Two Stage Method

- Fit each individual profile
- find mean of estimates:
  $\mu = \frac{1}{N}\sum_{i=1}^{N} q_i$
- find covariance of estimates:
  $Cov(x, y) = E[xy] - \mu_x \mu_y$

Fits



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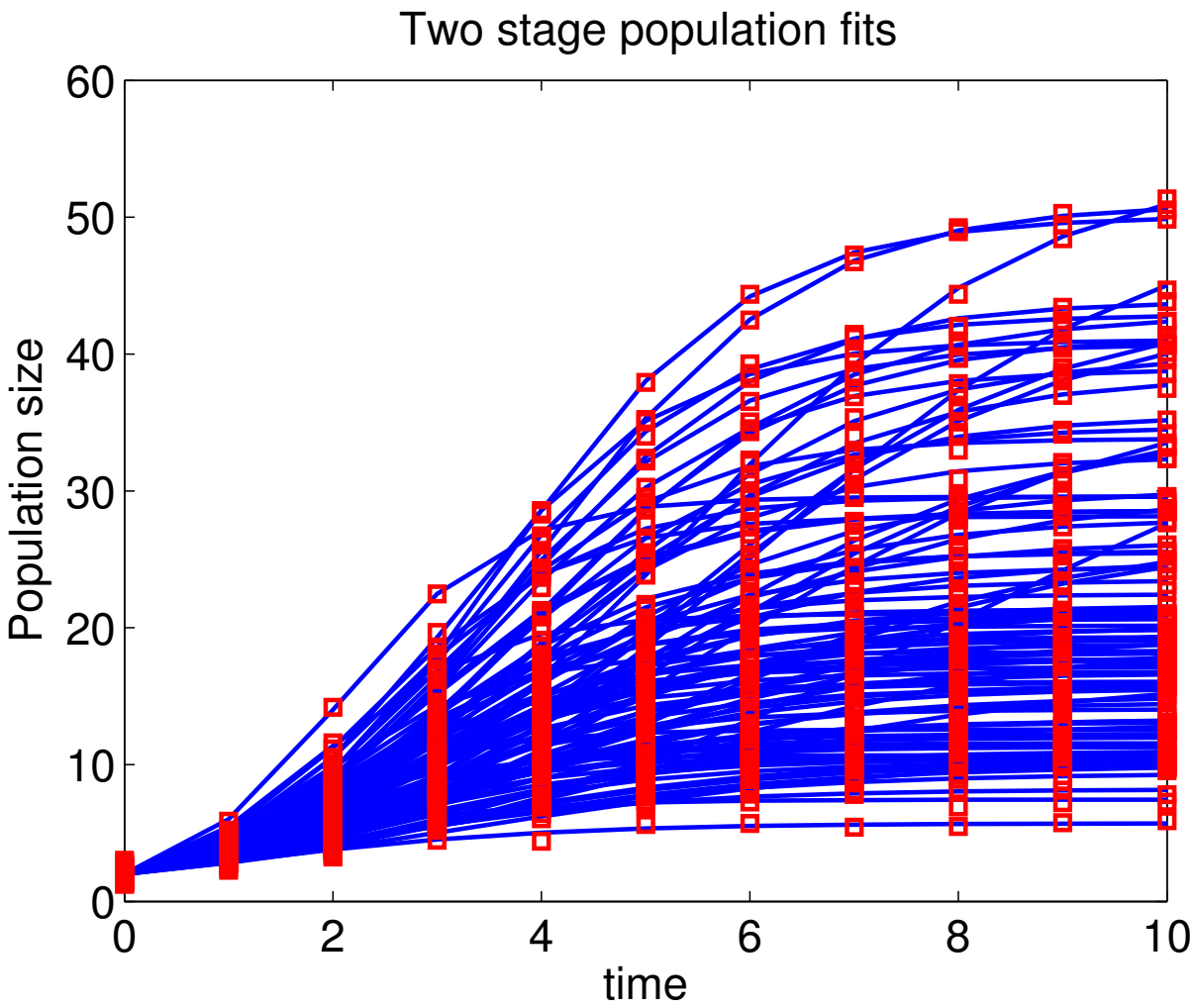
Two stage fits



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True

$$\begin{pmatrix} r \\ K \end{pmatrix} = \begin{pmatrix} 0.725 \\ 20 \end{pmatrix}$$

$$\Omega = \begin{pmatrix} 0.05 & 0 \\ 0 & 0.2 \end{pmatrix}$$

Two Stage Results

$$\begin{pmatrix} r \\ K \end{pmatrix} = \begin{pmatrix} 0.7551 \\ 23.168 \end{pmatrix}$$

$$\Omega = \begin{pmatrix} 0.056 & -0.0014 \\ -0.0014 & 0.2552 \end{pmatrix}$$

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Can we do better?

Nonlinear Mixed Effects Models

Nonlinear mixed effects models (*Davidian/Giltinan95*; *Wu/Zhang06*) are statistical models that are used to analyze repeated measure data, and a modeling framework involving both fixed-effects for population parameters and random effects incorporating uncertainty associated with inter- and intra-individual variability.

- **Stage 1:**(intra-individual variability - *assay errors, model errors*)

$$y_{i,j} = g(x_{i,j}, \phi_i) + e_{i,j}, \quad e_{i,j} \sim N(0, \sigma^2) \quad i = 1, ..., N, j = 1, ..., n_i$$

$$\frac{dx}{dt} = f(t, x, u; \phi), \quad x(0) = x_0$$

- **Stage 2:** (inter-individual variability)

$$\phi_i = h(\theta, Z_i, \eta_i); \quad \text{(log-normal)} \ \phi_i = \theta \exp(\eta_i), \quad \eta_i \sim N(0, \Omega)$$

Estimate population parameters: $(\theta, \sigma^2, \Omega)$

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Maximum Likelihood Estimation

Maximum likelihood estimation is a method to estimate parameters $(\theta, \sigma^2, \Omega)$ in a statistical model. Maximizing likelihood maximizes the probability of the observed data under the resulting distribution. Maximize the marginal density

$$L(\theta, \sigma^2, \Omega) \propto \prod_{i=1}^{N} \int p_1(\mathcal{Y}_{in_i}|\eta_i, \theta, \sigma^2) p_2(\eta_i|\Omega) d\eta_i$$

where L is the population likelihood function, $\mathcal{Y}_{ij} = [y_{i1}, ..., y_{in_i}]$ represents all observations of the ith individual up to time t_{ij}.

$$L(\theta, \sigma^2, \Omega) \propto \prod_{i=1}^{N} \int p_1(\mathcal{Y}_{in_i}|\eta_i, \theta, \sigma^2, d_i) p_2(\eta_i|\Omega) d\eta_i$$

Assuming a *normal conditional density*, the first stage distribution is

$$p_1(y_{in_i}|\eta_i, \theta, \sigma^2, d_i) \approx \prod_{j=1}^{n_i} \frac{exp(-\frac{1}{2} e_{i,j}^T R_{i(j|j-1)}^{-1} e_{i,j})}{\sqrt{|2\pi R_{i(j|j-1)}|}},$$

where $e_{i,j} = y_{i,j} - g(x_{i,j}, \phi_i)$ and $R_{i(j|j-1)} =$ prediction covariance.

The second stage distribution is

$$p_2(\eta_i|\Omega) \approx N(0, \Omega)$$

$$L(\theta, \sigma^2, \Omega) \propto \prod_{i=1}^{N} \int p_1(\mathcal{Y}_{in_i}|\eta_i, \theta, \sigma^2, d_i) p_2(\eta_i|\Omega) d\eta_i$$
$$= \prod_{i=1}^{N} \int \exp(l_i) d\eta_i,$$

a posteriori log-likehood function for a random effect of the ith individual

$$l_i = -\frac{1}{2} \sum_{j=1}^{n_i} \left(e_{ij}^T R_{i(j|j-1)}^{-1} e_{ij} + log|2\pi R_{i(j|j-1)}| \right) - \frac{1}{2} \eta_i^T \Omega^{-1} \eta_i - \frac{1}{2} log|2\pi\Omega|$$

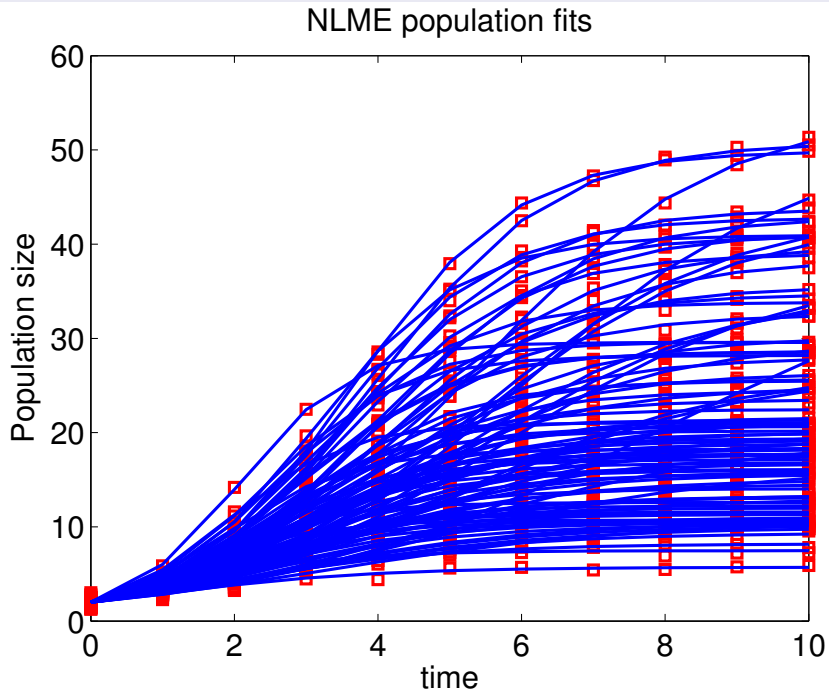
Logistic Equation

True vs. NLME

$$\begin{pmatrix} r \\ K \end{pmatrix} = \begin{pmatrix} 0.725 \\ 20 \end{pmatrix} \text{ vs. } \begin{pmatrix} r \\ K \end{pmatrix}_{\text{NLME}} = \begin{pmatrix} 0.735 \\ 20.46 \end{pmatrix}$$

$$\Omega = \begin{pmatrix} 0.05 & 0 \\ 0 & 0.2 \end{pmatrix} \text{ vs. } \Omega_{\text{NLME}} = \begin{pmatrix} 0.055 & -0.0018 \\ -0.0018 & 0.255 \end{pmatrix}$$

Fits



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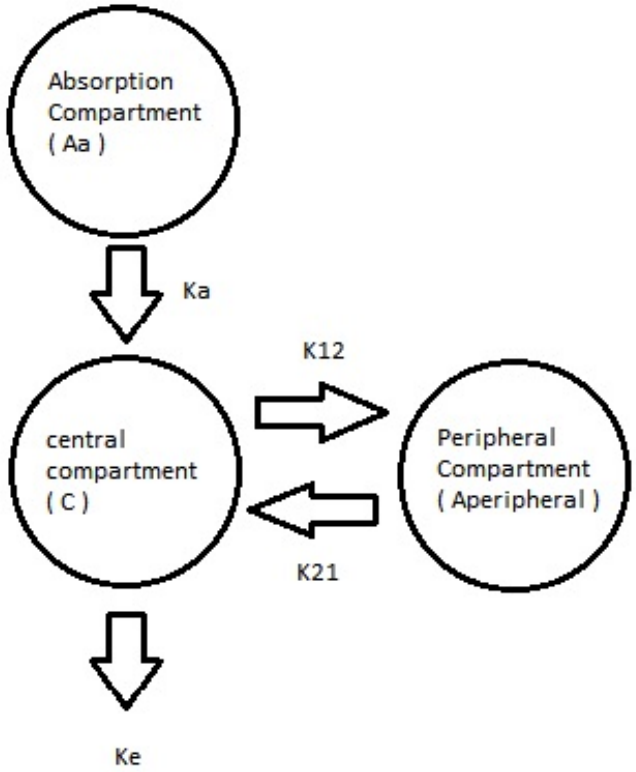
Population Pharmacokinetic Study of Metformin

Metformin is a commonly prescribed treatment for type 2 diabetes, with a poorly understood glucose-lowering action. A 16 subject study of a new 2000mg extended release (XR) single dose oral formulation of metformin was carried out and plasma concentrations were collected over a 36 hour time frame (every half hour (first 3 hours and between hours 12 to 14); otherwise, every hour).

A Two Compartment Oral Absorption Model

A simple two compartment model is used to describe the pharmacokinetics model of the single dose oral administration of Metformin.



Two Compartment Oral Absorption - Model

$$\frac{d}{dt}\begin{pmatrix} A_a \\ C \\ A_{peripheral} \end{pmatrix} = \begin{pmatrix} -k_a & 0 & 0 \\ \frac{k_a}{V} & -(k_{12}+k_e) & \frac{k_{21}}{V} \\ 0 & k_{12}V & -k_{21} \end{pmatrix}\begin{pmatrix} A_a \\ C \\ A_{peripheral} \end{pmatrix}$$

with observation equation

$$log(C_{obs}) = log(C) + e, \qquad e \sim N(0, \sigma^2)$$

Individual parameter vector (rate constants)

$$\phi_i = \theta \exp(\eta_i), \quad \eta_i \sim N(0, \Omega)$$

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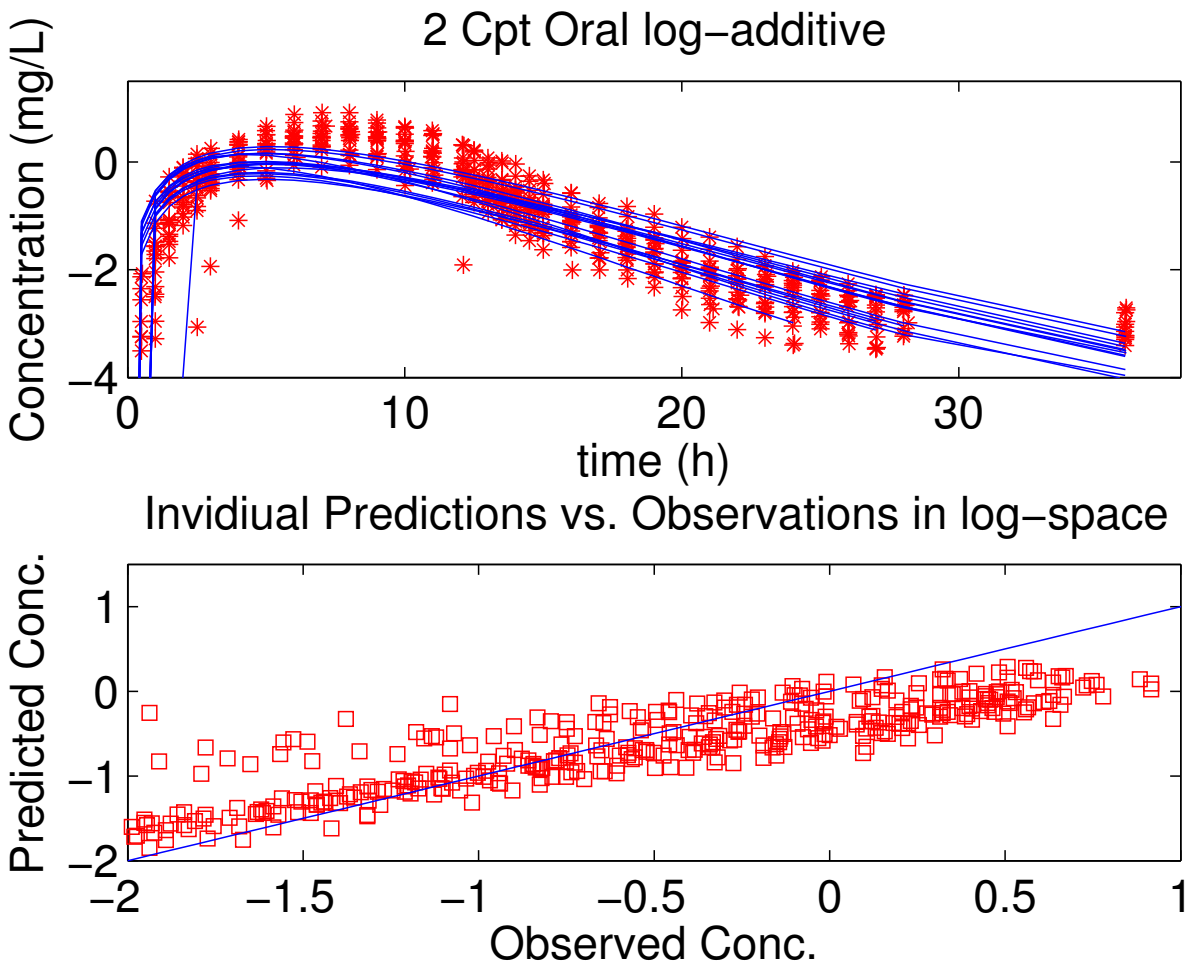
NLME population PK



How do we refine the model?

Decompose the intra-individual variability into two components:

- model misspecification term representing the uncertainty associated with unknown or incorrectly specified dynamics

$$dx = f(x, u, t, \phi)dt + \sigma dw$$

- measurement noise term

Nonlinear Filtering

NLME - revisited

The population likelihood

$$L(\theta, \sigma^2, \Omega) \propto \prod_{i=1}^{N} \int p_1(\mathcal{Y}_{in_i}|\eta_i, \theta, \sigma^2, d_i) p_2(\eta_i|\Omega) d\eta_i$$

where the first stage distribution is

$$p_1(y_{in_i}|\eta_i, \theta, \sigma^2, d_i) \approx \prod_{j=1}^{n_i} \frac{exp(-\frac{1}{2} e_{i,j}^T R_{i(j|j-1)}^{-1} e_{i,j})}{\sqrt{|2\pi R_{i(j|j-1)}|}},$$

Filtering Integration: (*Overgaard05*)

$$R_{i(j|j-1)} = H_{ij} P_{i(j|j-1)} H_{ij}^T + \sigma^2$$
$$\hat{y}_{i(j|j-1)} = g(\bar{x}_{i(j|j-1)}, \phi_i)$$

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Two-Compartment Absorption Model- revisited

Due to variable absorption, use a stochastic differential equation (SDE) model

$$d\begin{pmatrix} k_a \\ A_a \\ C \\ A_{peri} \end{pmatrix} = \begin{pmatrix} 0 \\ -k_a A_a \\ \frac{k_a}{V} A_a - (k_{12} + k_e) C + \frac{k_{21}}{V} A_{peri} \\ k_{12} VC - k_{21} A_{peri} \end{pmatrix} dt + \begin{pmatrix} \sigma_{k_a} & 0 & 0 & 0 \\ 0 & \sigma_{A_a} & 0 & 0 \\ 0 & 0 & \sigma_{central} & 0 \\ 0 & 0 & 0 & \sigma_{peri} \end{pmatrix} dw_t$$

SDE Model Calibration

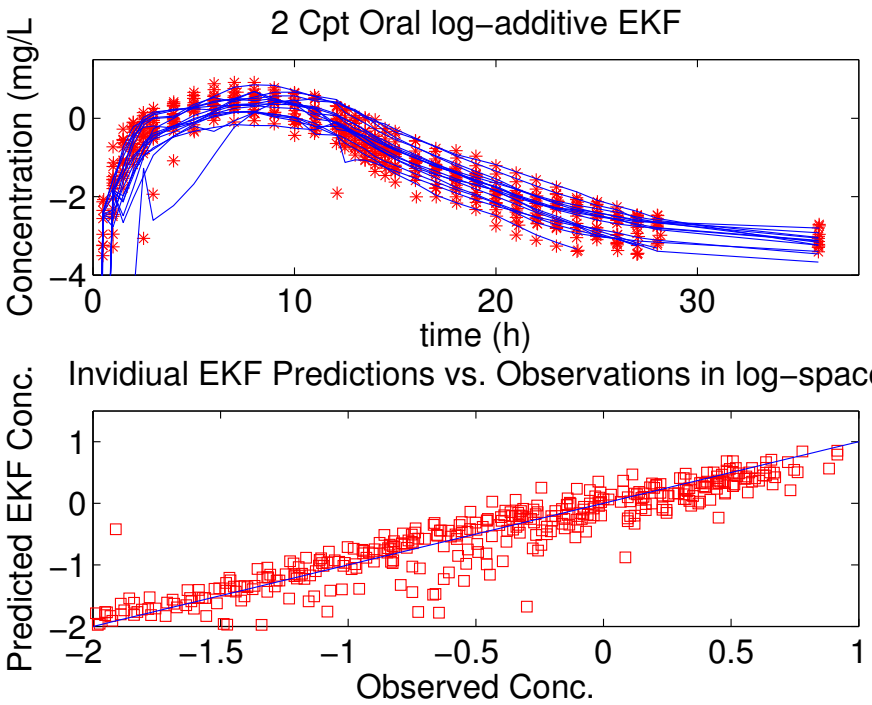


Figure: SDE Model Fit: EKF

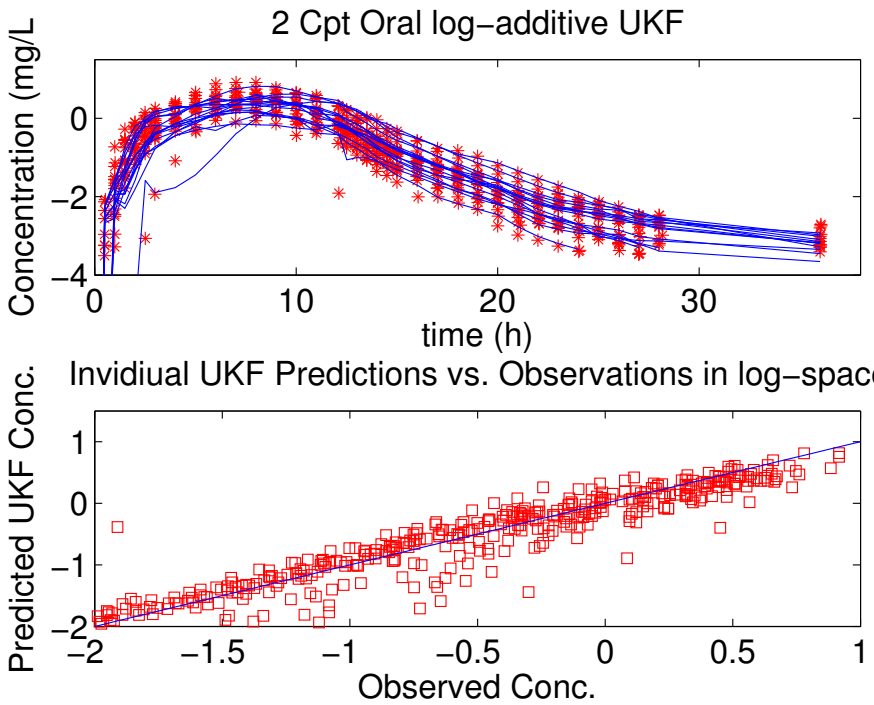


Figure: SDE Model Fit: UKF

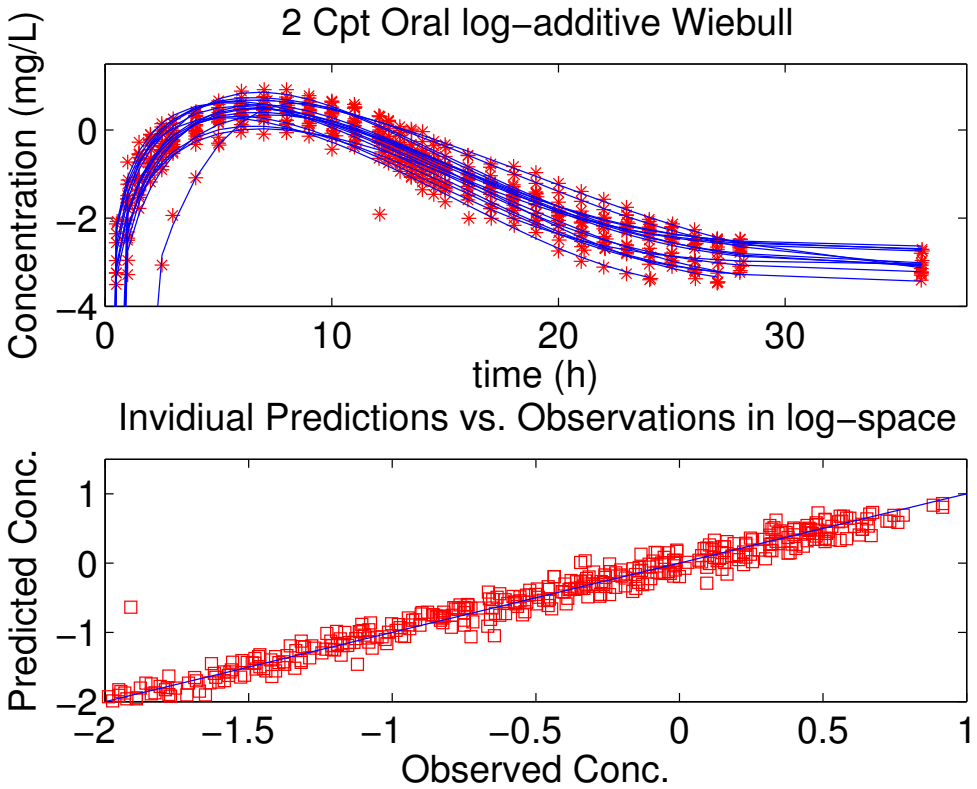
A Structured Model for Absorption Rate

Utilizing information from the SDE model, a structural model for absorption rate (Wiebull) is considered:

$$k_a = \alpha\big(1 - exp(-(\lambda/t)^K)\big)$$

$$\frac{d}{dt}\begin{pmatrix} A_a \\ C \\ A_{peripheral} \end{pmatrix} = \begin{pmatrix} -k_a & 0 & 0 \\ \frac{k_a}{V} & -(k_{12}+k_e) & \frac{k_{21}}{V} \\ 0 & k_{12}V & -k_{21} \end{pmatrix}\begin{pmatrix} A_a \\ C \\ A_{peripheral} \end{pmatrix}$$

Wiebull Model Calibration



SDE Model Calibration

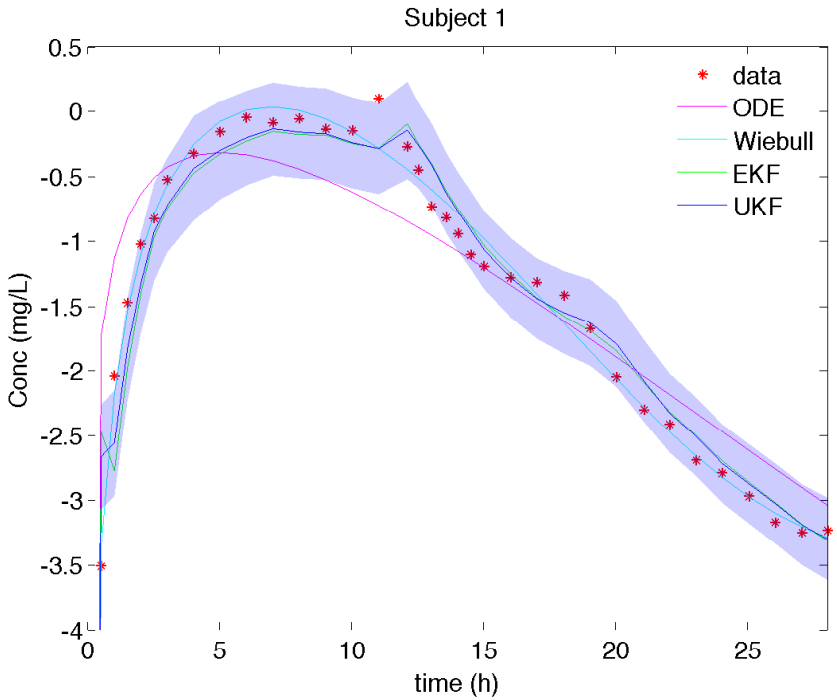


Figure: Subject one fits

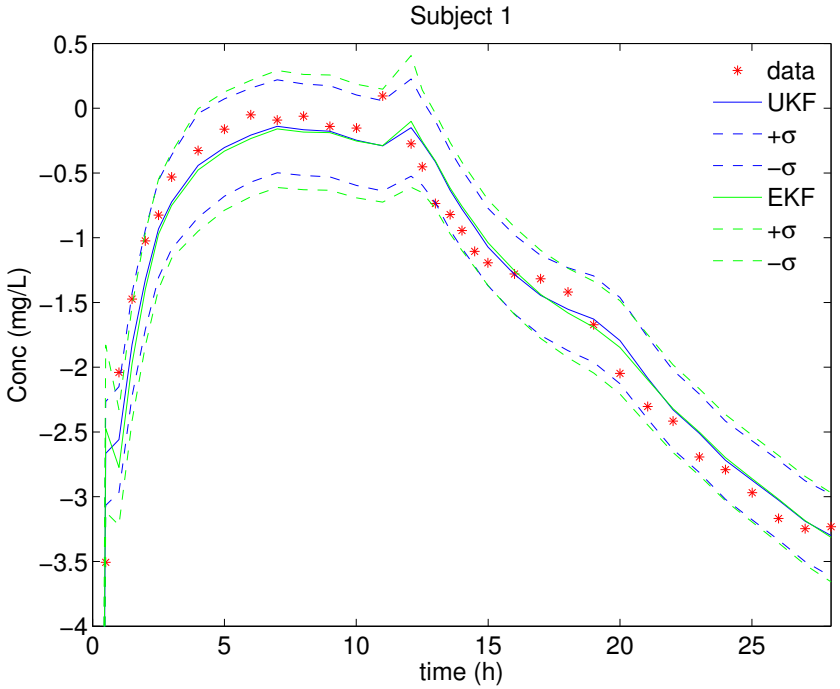


Figure: EKF vs. UKF prediction intervals

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Conclusion

- Noise in Biology can present itself in many ways and the proper handling of this noise is important for both the methodologies and the modeling process.
- The use of nonlinear filters for the estimation of both state and parameters has shown encouraging results and presents advantages to classical approaches (ODE) in the context of nonlinear mixed effects model.