

Time-dependent random effects

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Introduction

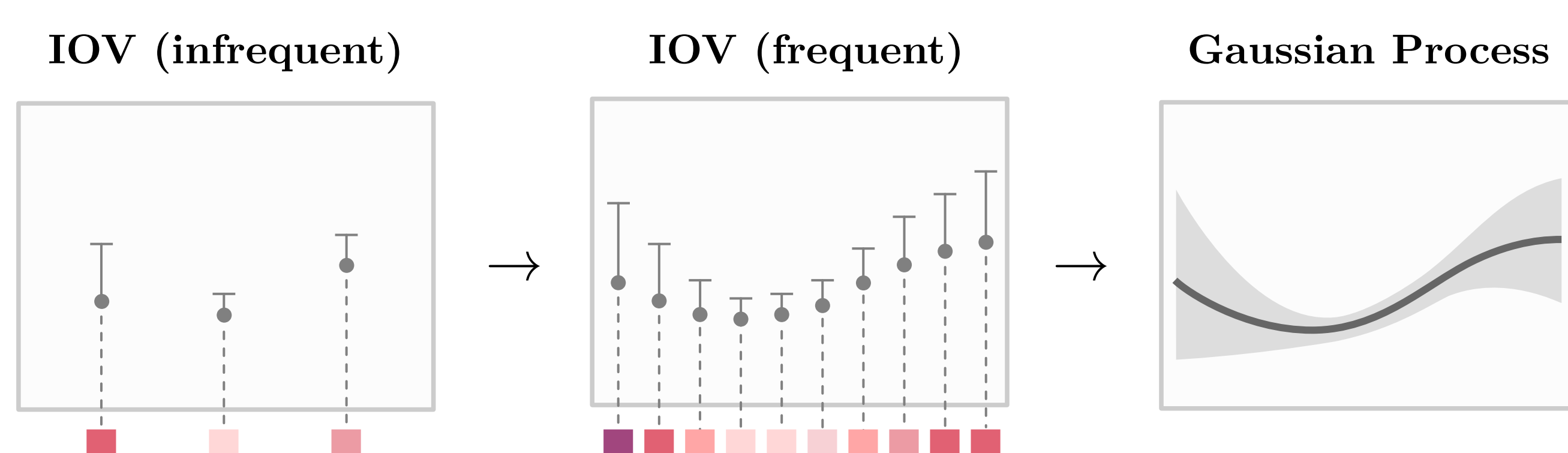
In mixed-effect models, random effects are used to explain inter-individual variability. Their effect is *constant over time*, which can be insufficient when PK changes following organ damage or due to drug-interactions. Usually such effects are represented by inter-occasion variability, but choosing the time interval when new occasions start is difficult.

Approach

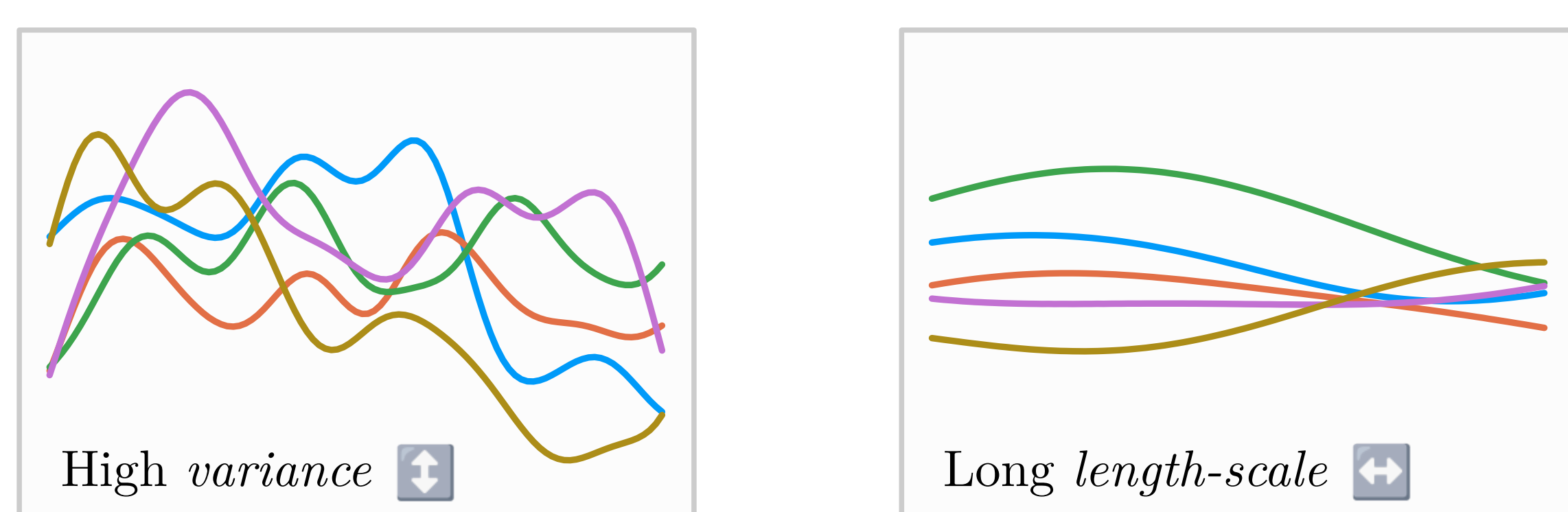
We suggest using *Gaussian Processes* (GPs) to learn time-dependent changes in PK (or PD) in continuous-time.

Gaussian Processes

GPs extend multivariate normal distributions into infinite dimensions:



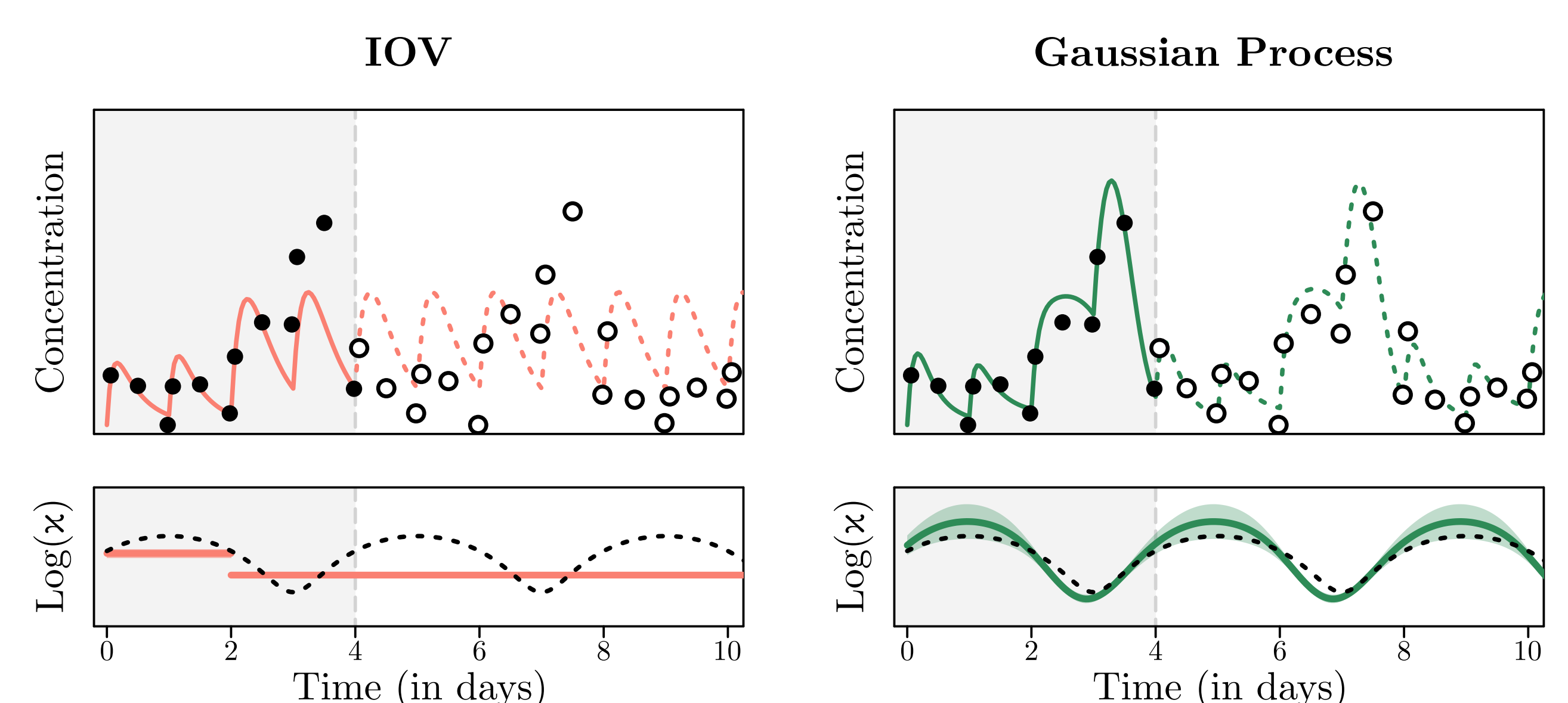
The covariance between points is described by a *kernel function*. This function describes the similarity of model predictions at different inputs:



Synthetic experiment

We simulate data ($n = 60$) from a one-compartment model with first-order elimination. A sinusoidal time-dependent effect $f(t) = \alpha \cdot \sin(2\pi t/96) + 1$ was added to k_{10} with varying amplitude $\alpha \sim \text{Beta}(4, 5)$ for each subject. A daily dose of 0.3 mg/kg was given for 14 subsequent days. Three measurements were collected every 1.5, 12, and 24 hours after administration. Models were trained on data from the first four days and accuracy was evaluated on the last ten days. Model parameters were optimized using Variational Expectation Maximization.

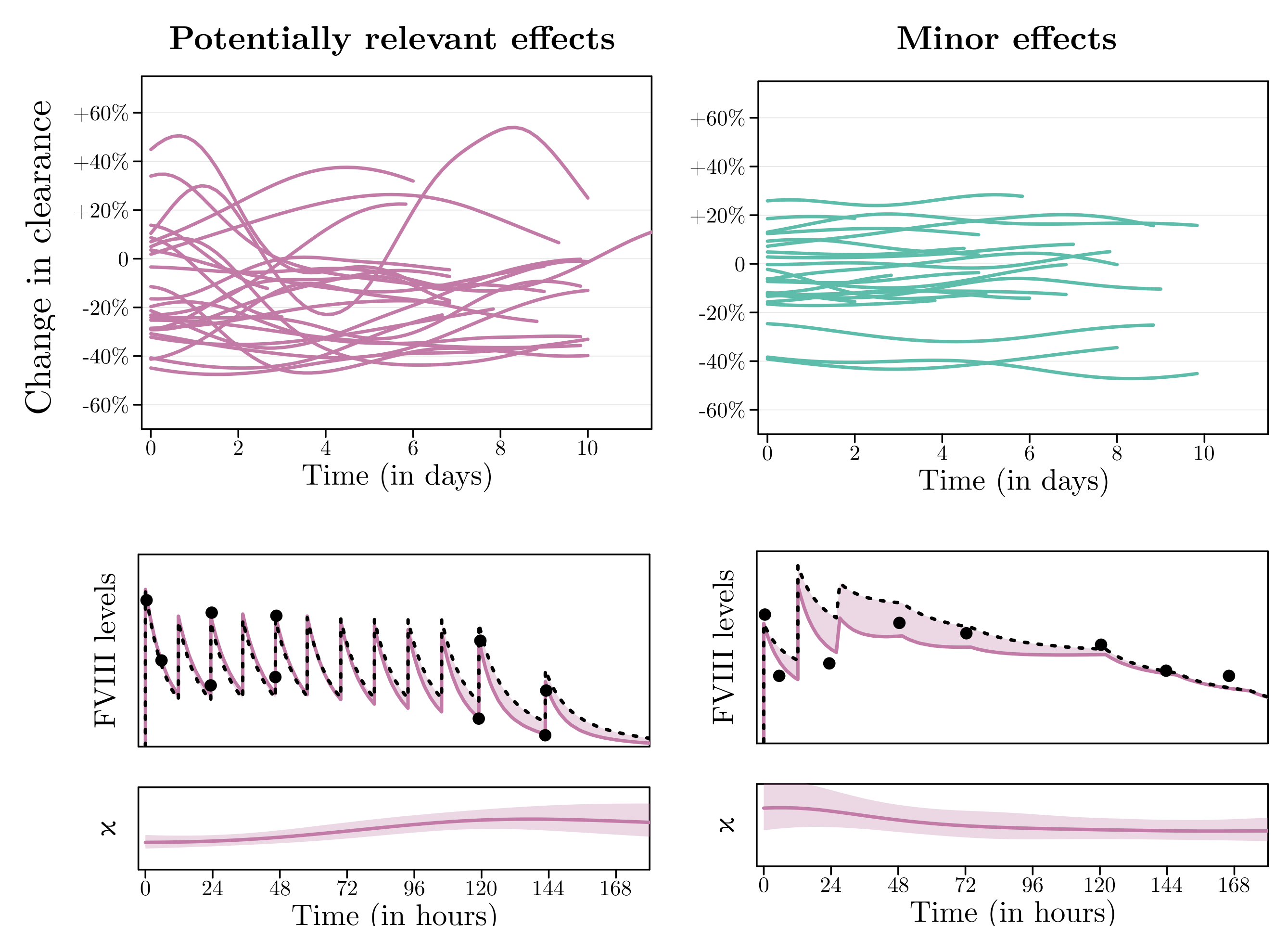
Results



Real-world experiment

We also evaluate the model on a real-world data of haemophilia A patients undergoing surgery ($n = 47$). We augment an existing population PK model with a time-dependent effect on clearance.

Results



Conclusions

GPs allow for the learning of prior distributions over latent effects, constraining the solution to follow learned patterns (reducing overfitting). Based on the real-world data, we found that time-dependent effects could be highly variable between subjects, indicating the challenge in estimating such effects using deterministic functions or typical effects. The GP posterior can be iteratively updated as more data becomes available, and the effect can be projected into the future while taking into account uncertainty over its trajectory.