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Motivation:

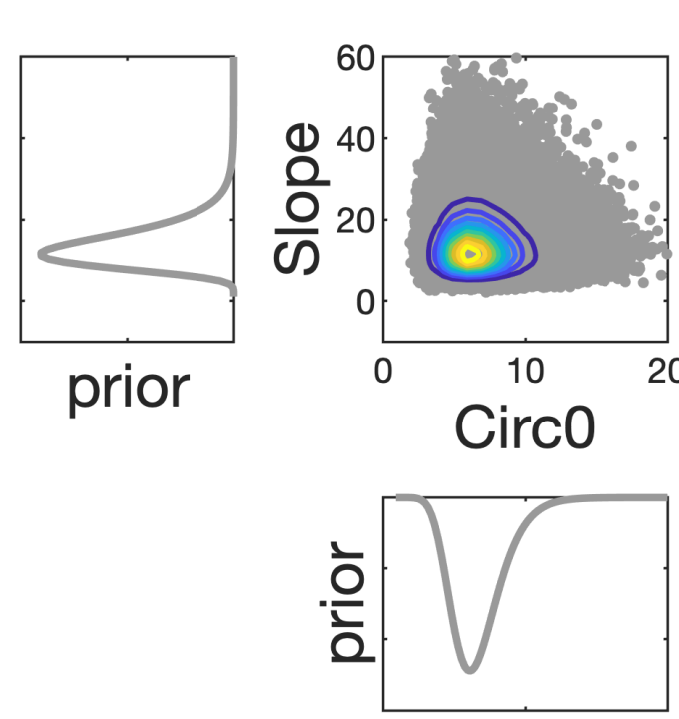
- Cytotoxic anticancer drugs have a narrow therapeutic window and high interindividual variability (IIV)
- Neutropenia is often the major dose-limiting toxicity but is also seen as surrogate for efficacy
- Typically, Bayesian forecasting tools for model-informed precision dosing (MIPD) use the most probable parameter estimate without measure of uncertainty [1,2]

Objectives:

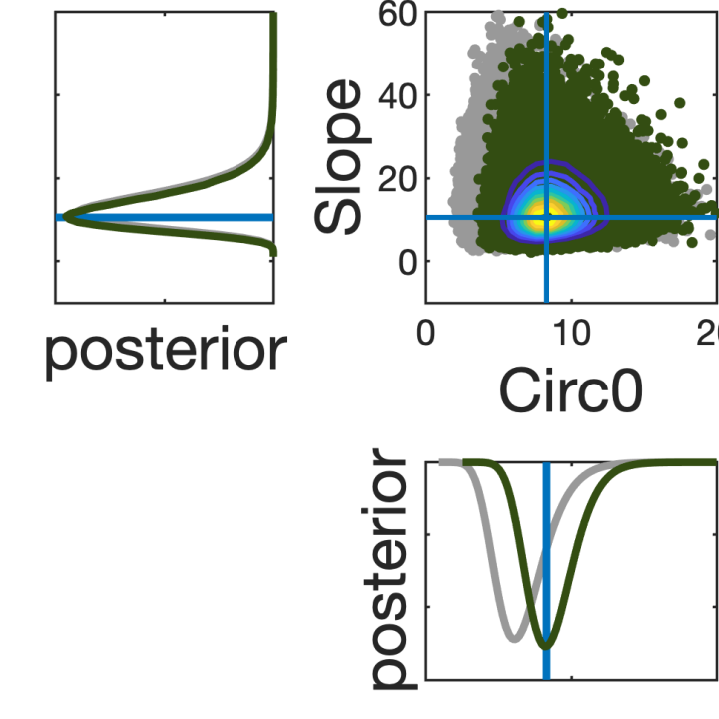
- Combine efficiently prior knowledge with therapeutic drug/biomarker monitoring (TDM) data, e.g. patient-specific drug concentrations or neutrophil counts
 - Identify patients at risk for toxic or too cautious dosing regimens
 - Quantify uncertainties for holistic risk analysis of subsequent dose adaptations
- Reliable, individual and computational efficient decision support in ongoing treatment

General workflow in MIPD using TDM data

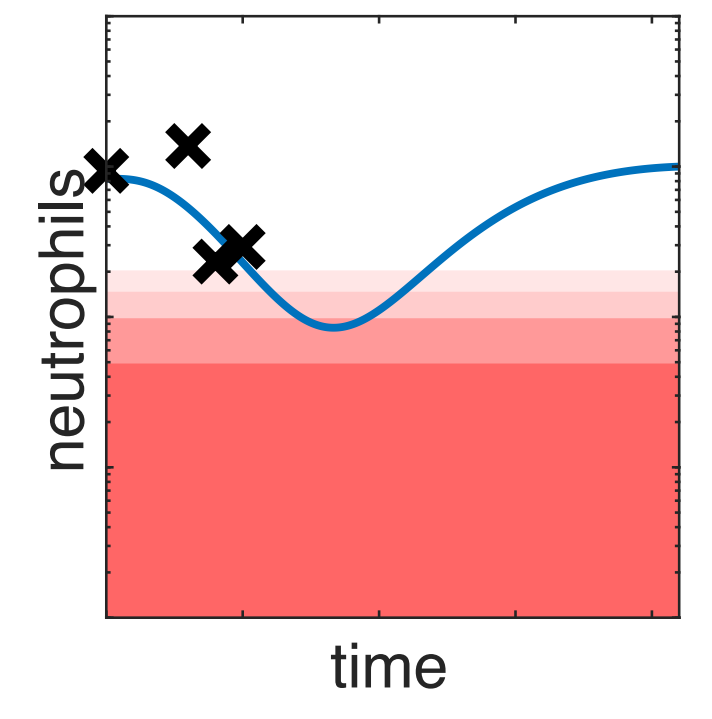
Population analyses of clinical studies [3,4] provide prior knowledge about the model parameters in the form of prior distributions. The uncertainty about the parameters is, thus, characterised by the unexplained IIV observed in clinical studies.



In therapeutic drug/biomarker monitoring (TDM) patient-specific data is collected during treatment. Bayes' formula combines prior knowledge with patient-specific data.



The posterior distribution entails all available knowledge about the individual parameters. In Bayesian forecasting the model predictions are typically based on the maximum a-posteriori (MAP) estimate, see e.g. [5].

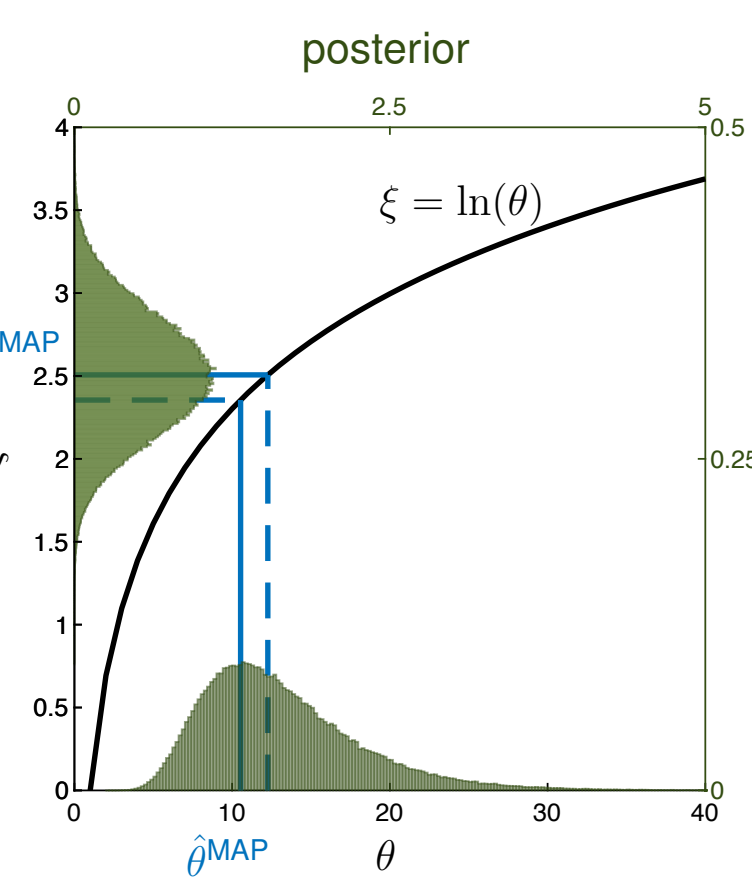


Limitations of MAP estimation

Dependence on parametrisation

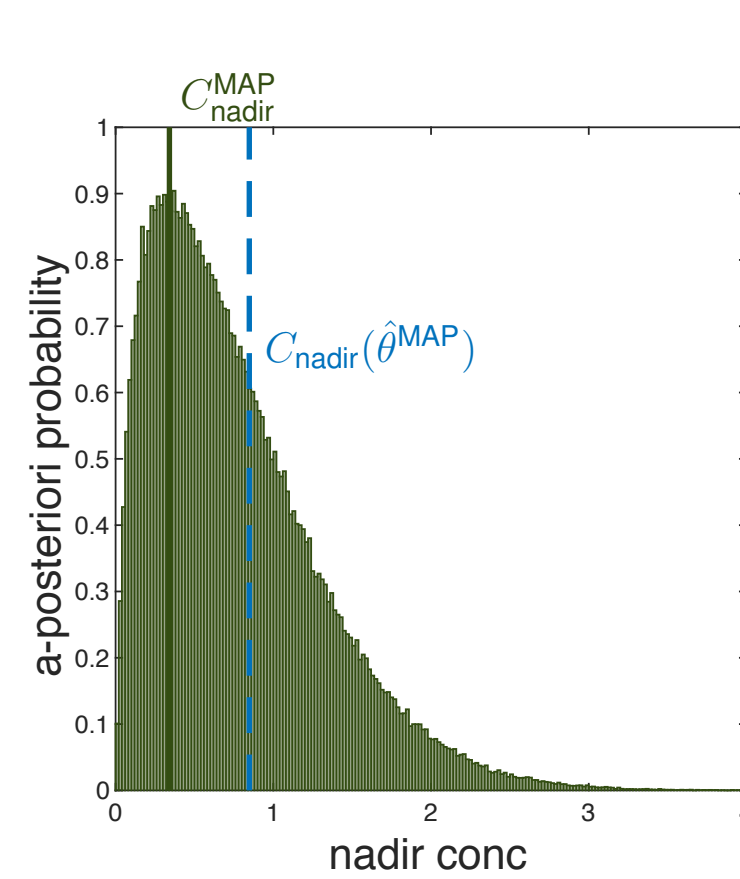
Probability densities behave differently compared to functions under a change of model parametrization [6,7]. Therefore, in general

$$\hat{\theta}^{\text{MAP}} \neq \exp(\hat{\xi}^{\text{MAP}})$$



Mode not preserved under transformation

The MAP-based prediction for a nonlinear model does not necessarily equal the most probable outcome under the current knowledge (posterior).

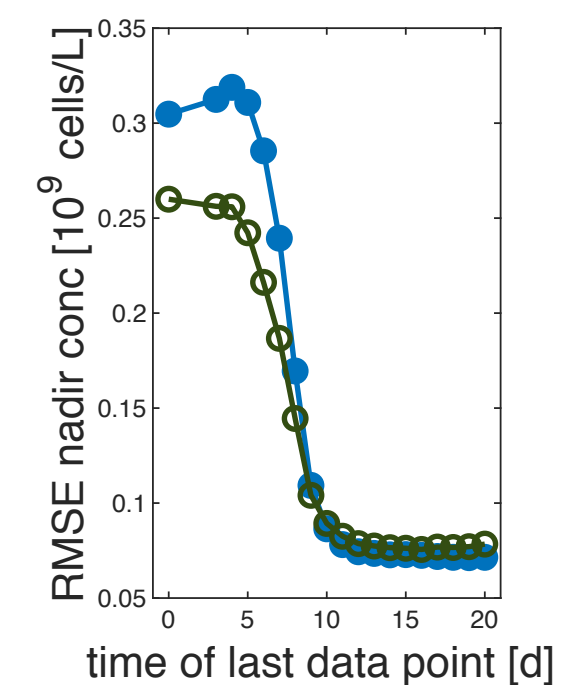


Reduced prediction accuracy for quantities of interest

The MAP-based prediction of quantities of interest $T(\theta)$ as point estimate had reduced prediction accuracy compared to the posterior expectation

$$\mathbb{E}[T(\theta)|y_{1:n}] = \int T(\theta)p(\theta|y_{1:n})d\theta$$

At the most relevant time point for prediction, in the beginning of the treatment cycles with only few available data points, the root mean squared error (RMSE) is lower for the full Bayes approach.

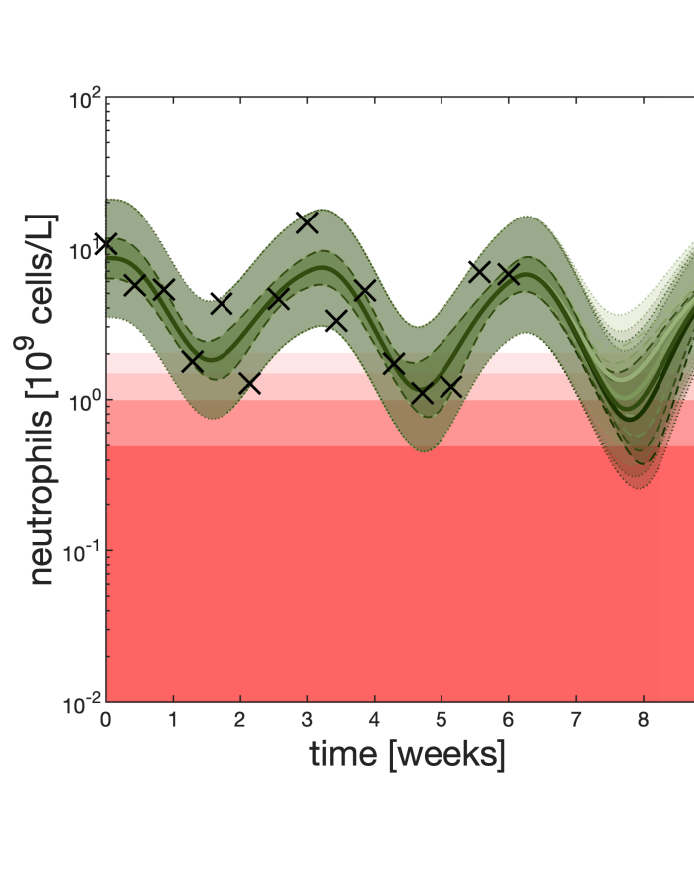


→ MAP estimation has several crucial drawbacks for reliable and accurate MIPD

More informative decision support by full Bayes

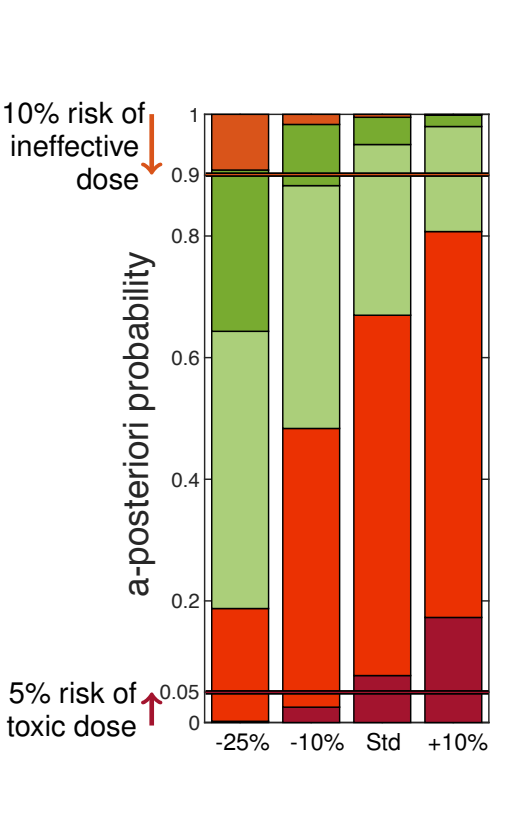
Credible intervals (CrIs) in observable space

CrIs provide a measure of confidence in the predicted outcome and additional information to discriminate between dosing scenarios (% change from standard dose).



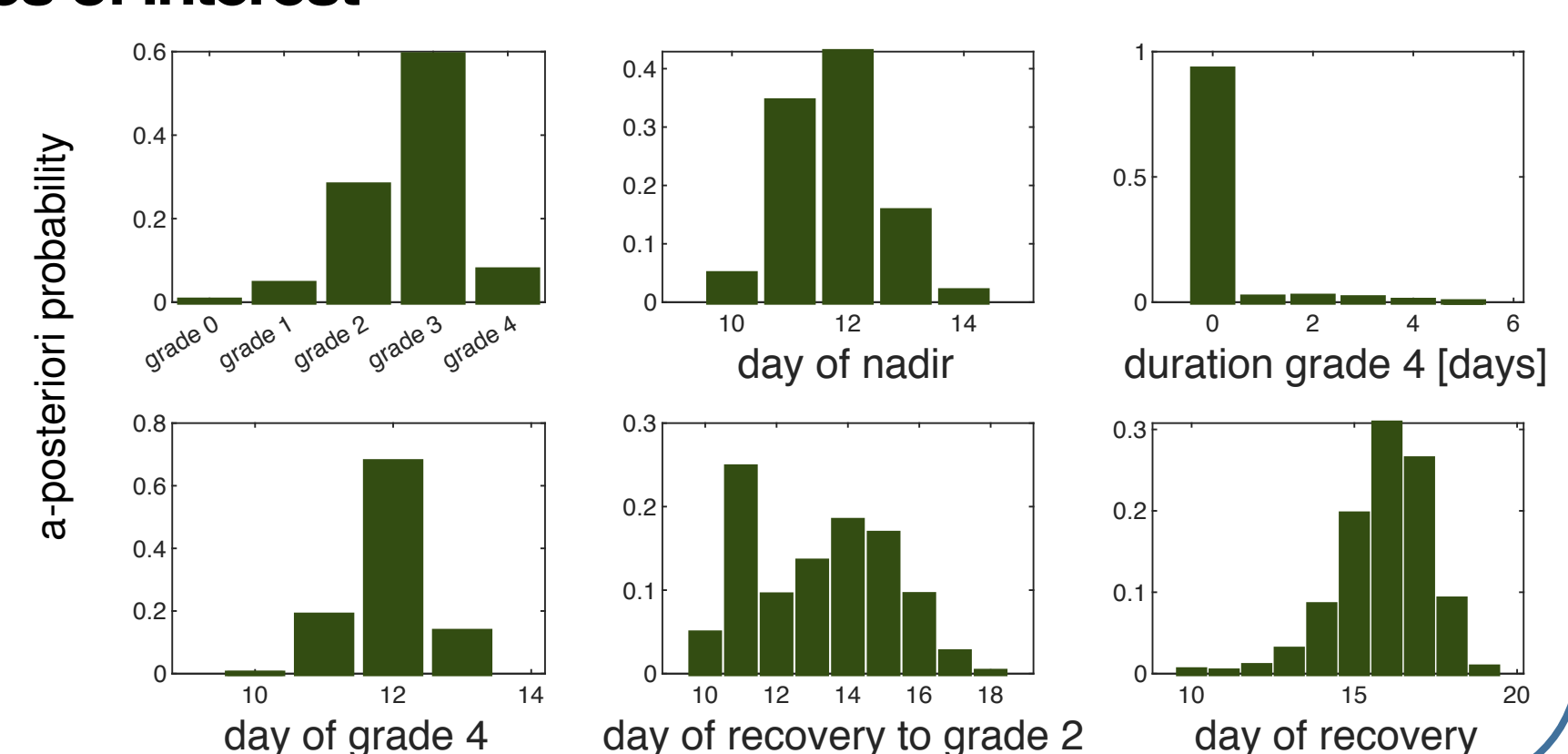
Simultaneous risk evaluation

Optimal dose can be found as well-informed trade-off between the risk of inefficacy and toxicity, which is simultaneously quantified in the tails of the posterior.



Probabilistic statements about quantities of interest

The derivation of the a-posteriori probabilities of all quantities of interest empowers the decision-making process as they provide a holistic picture of the overall situation since involved risks are determined comprehensively.



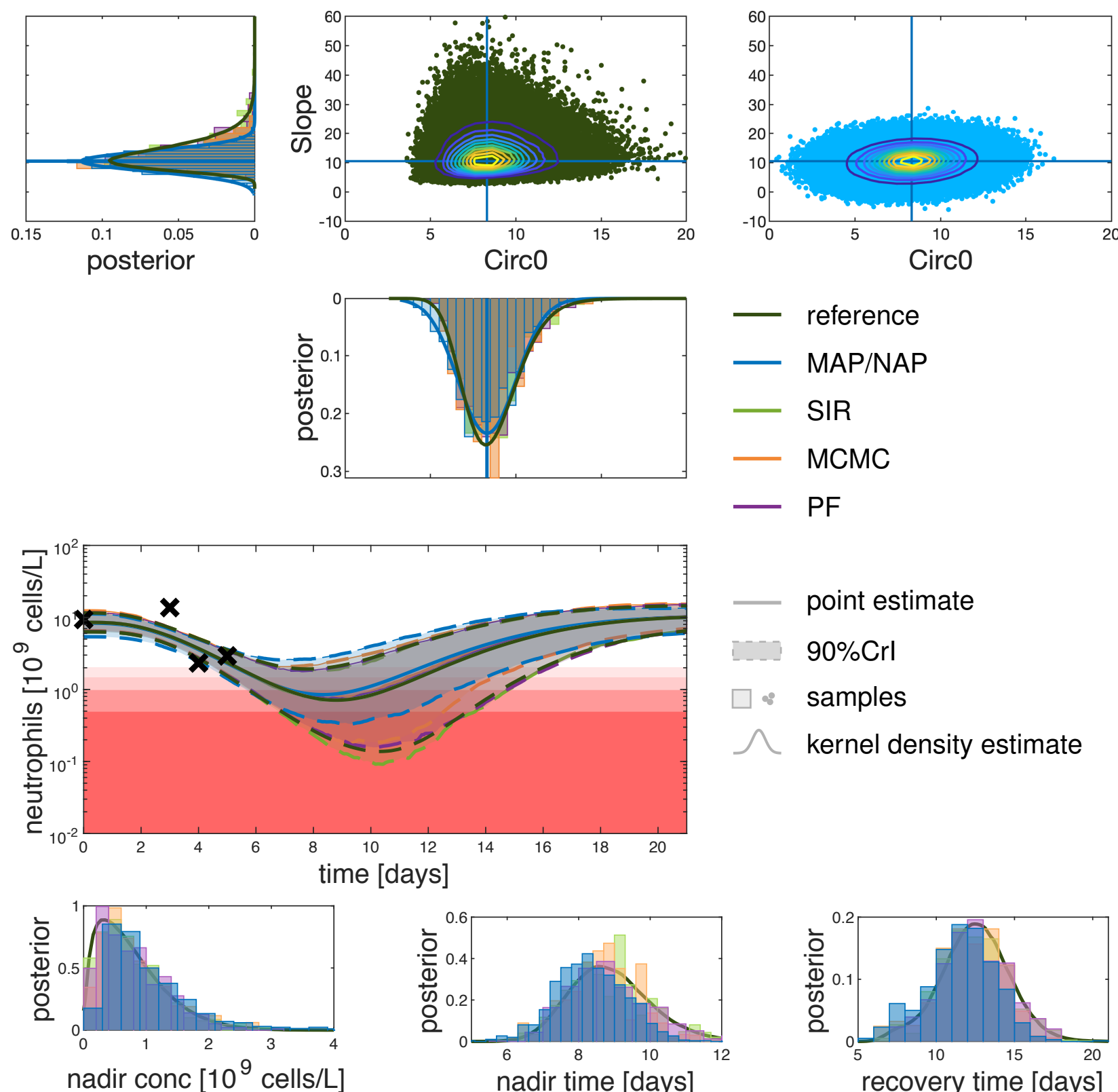
Low cost approximation techniques for uncertainty quantification

We considered the following approximations to the posterior

- Normal approximation (NAP)**
local approximation at the mode of the posterior (MAP estimate)
- Sampling Importance Resampling (SIR)**
samples from importance distribution (prior) are corrected via importance weights and then resampled [8,9]
- Markov chain Monte Carlo (MCMC)**
Metropolis-Hastings sampler [10] with adaptive proposal (prior or previous posterior)
- Particle filter (PF)**
sequential data assimilation method based on sequential Bayes' formula

$$p(\theta|y_{1:n}) \propto p(y_n|y_{1:n-1}, \theta) \cdot p(\theta|y_{1:n-1}),$$

with previous posterior as prior for the current update [11].

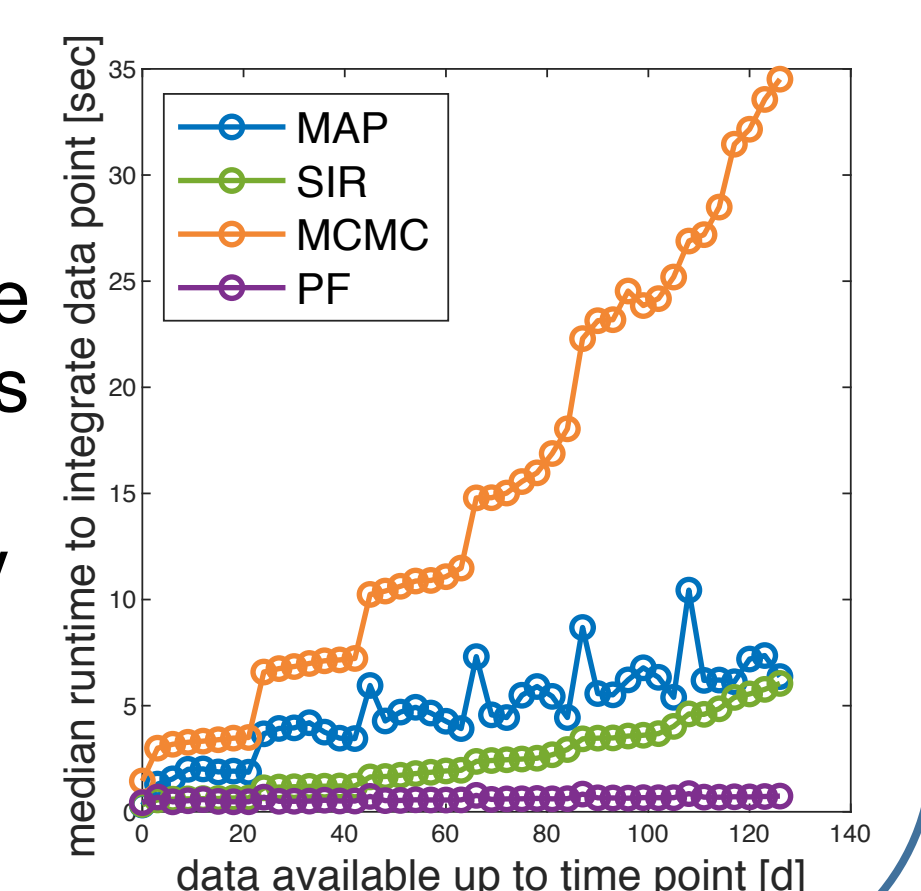


NAP: unreliable for skewed distributions

- Underestimating the risk of severe neutropenia
- sampling can lead to negative/unphysiological values
- asymptotic normality of posterior only for informative data

PF: Efficient real-time processing of patient data

- only the current data point is needed for updating the posterior
- constant computational effort over time
- data does not need to be stored for future analysis
- Implementation of inter-occasion variability is facilitated as model equations do not need to be integrated over all occasions



Conclusion:

Fully Bayesian approaches overcome drawbacks of MAP estimation by approximating the full posterior distribution

- more accurate point estimates
- comprehensive uncertainty quantification
- probabilistic statements about different possible outcomes

Open research questions:

- Continuous learning with every patient: update prior knowledge for next patient with posterior of current patient → hierarchical Bayes
- Real-time dose optimisation within integrated learning framework taking into account relevant factors → high dimensional optimisation under uncertainty

References:

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