

Improving model-based predictions of neutropenia using sequential data assimilation

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Motivation:

- “20 of 100 [chemotherapy] patients are not fit for their next scheduled treatment”[1]
- Narrow therapeutic window and high interindividual variability
- Novel digital healthcare device [1] allows frequent neutrophil monitoring at home
- Reliable individualised predictions of the neutrophil time-course could enable individualised dosing schedules for subsequent treatments

Objectives:

- Combine prior knowledge with patient-specific neutrophil counts in real time
 - Identify patients at risk for toxic or subtherapeutic dosing regimens
 - Predict whether recovery is reached before subsequent treatment
- Provide individual decision support in ongoing treatment

Prior knowledge

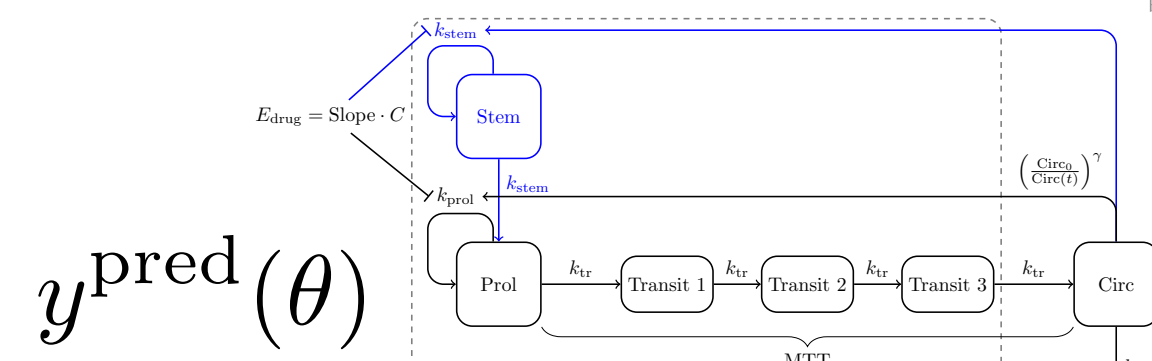
Population analysis [2] based on clinical study [3]

→ Prior distribution based on patient covariates (co) $p(\theta|\theta^{TV}(\text{co}), \Omega)$



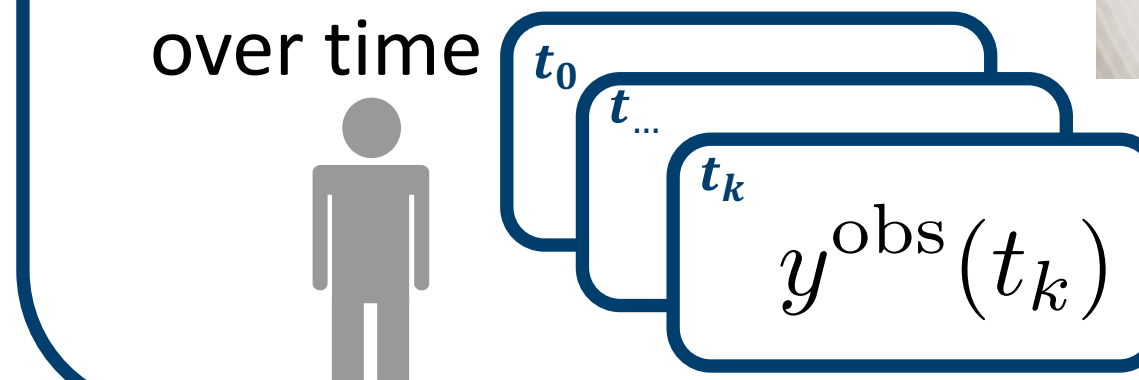
Model [2] describing drug effect on hematopoietic system

→ Prediction $y^{\text{pred}}(\theta)$



Patient specific real-time data from digital health care device [1]

→ Neutrophil counts over time



Recursive update based on Bayes' formula:

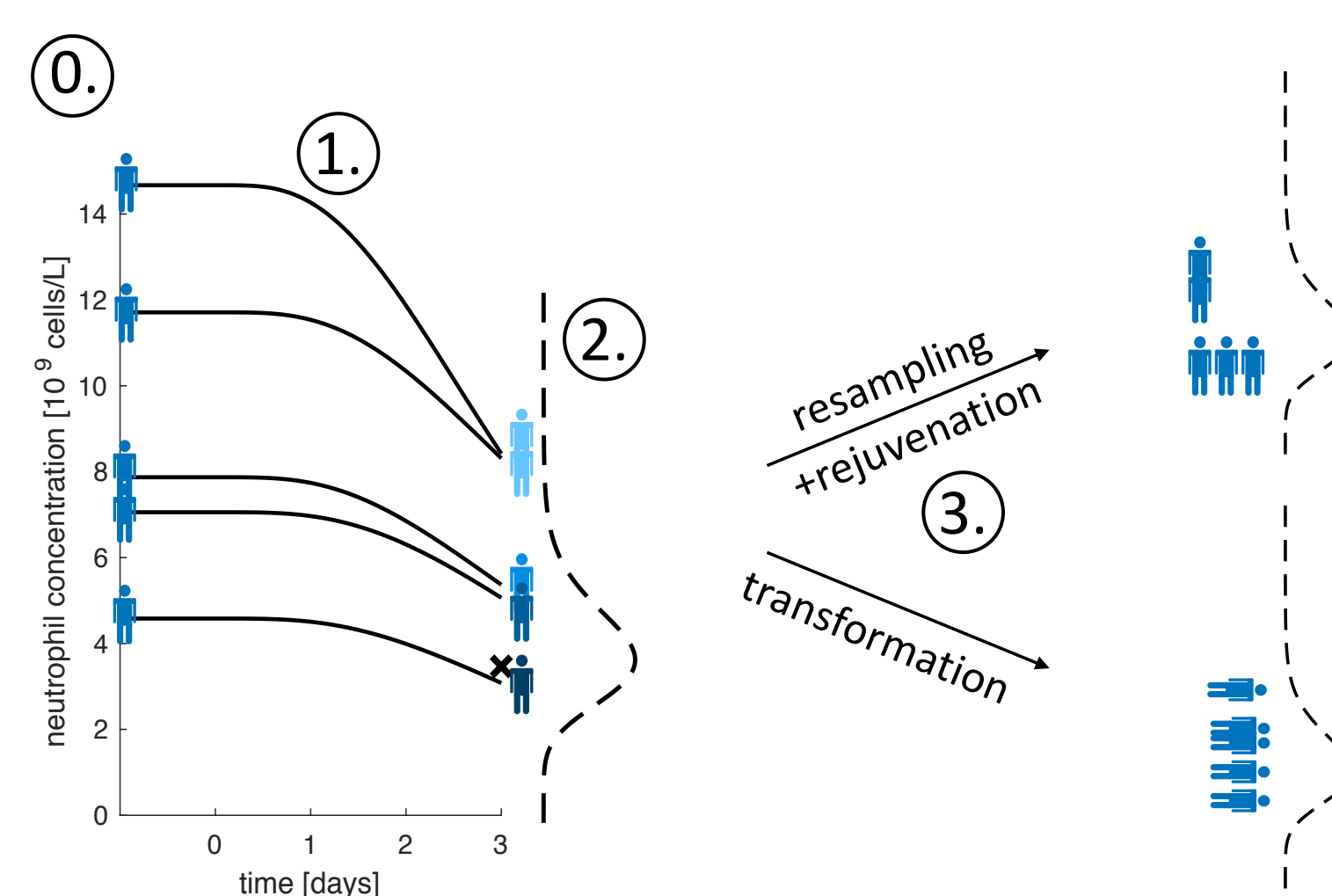
$$p(\theta|y_1^{\text{obs}}) \propto p(y_1^{\text{obs}}|\theta, \sigma^2) \cdot p(\theta|\theta^{TV}(\text{co}), \Omega)$$

$$p(\theta|y_{1:k}^{\text{obs}}) \propto p(y_k^{\text{obs}}|y_{1:k-1}^{\text{obs}}, \theta, \sigma^2) \cdot p(\theta|y_{1:k-1}^{\text{obs}})$$

Methods

Sequential data assimilation

- Particle filter (PF) (or sequential Monte Carlo)
- Suitable for non-Gaussian error models and non-linear structural models
- Monte Carlo approximation of the posterior based on importance sampling
- Particles $\triangleq$ population of virtual individuals with same covariates and individual weighting factor
- 0. Initialization of particles $\{x_{i0}, \theta_{i0}, w_{i0}\}_{i=1}^{n_{\text{particles}}}$
Sampling of initial states and parameters from prior distributions
Uniform weighting factors for all particles $w_{i0} = 1/n_{\text{particles}}$
- 1. Model propagation
Propagation of states according to model equations $x_{ik} \leftarrow x_{ik-1}, \theta_{ik-1}$
- 2. Data assimilation
Update weighting factors proportional to the likelihood $\tilde{w}_{ik} = p(y_k^{\text{obs}}|x_{ik}, \theta_{ik}) \cdot w_{ik-1}$
Normalize weighting factors $w_{ik} = \tilde{w}_{ik} / \sum_i \tilde{w}_{ik}$
- 3. Resampling + rejuvenation $\theta_{ik+1} = \theta_{ik} + \xi_{ik}$, $\xi_{ik} \sim \mathcal{N}(0, W)$ or transformation $z_{jk}^a = \sum_{i=1}^{n_{\text{particles}}} z_{ik}^f d_{ij}(t_k)$, where $z = (x, \theta)^T$ to counteract degeneracy [4]



Maximum a-posteriori (MAP) estimation

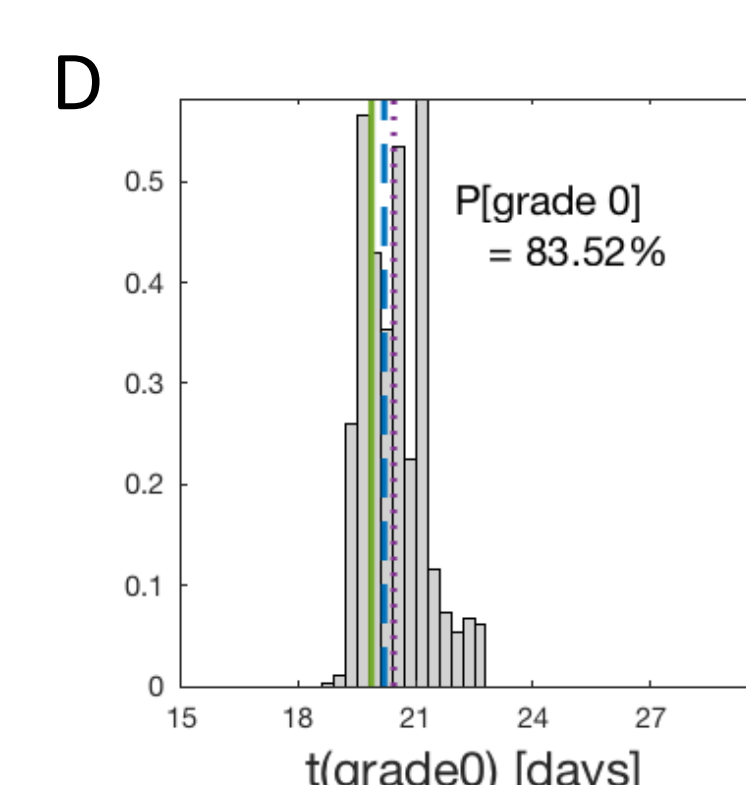
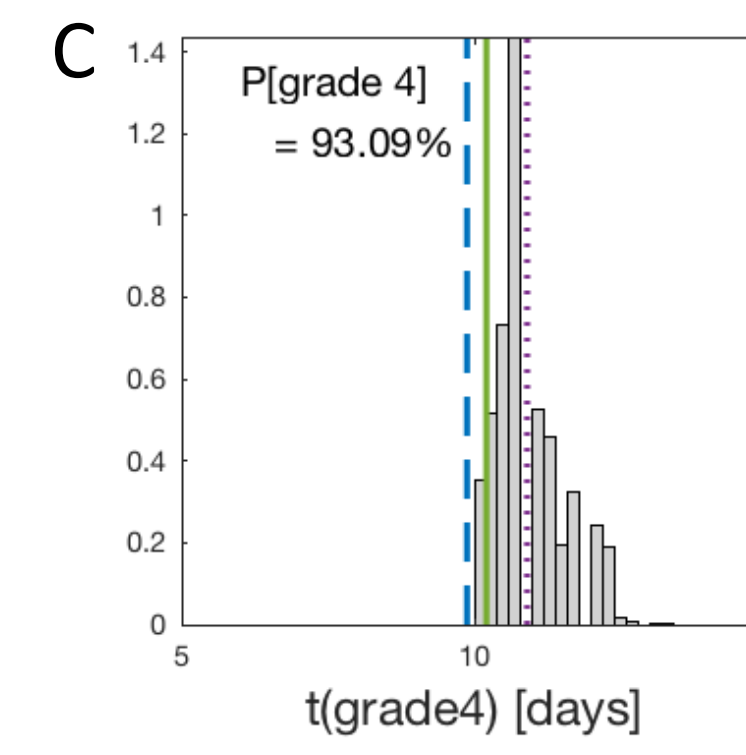
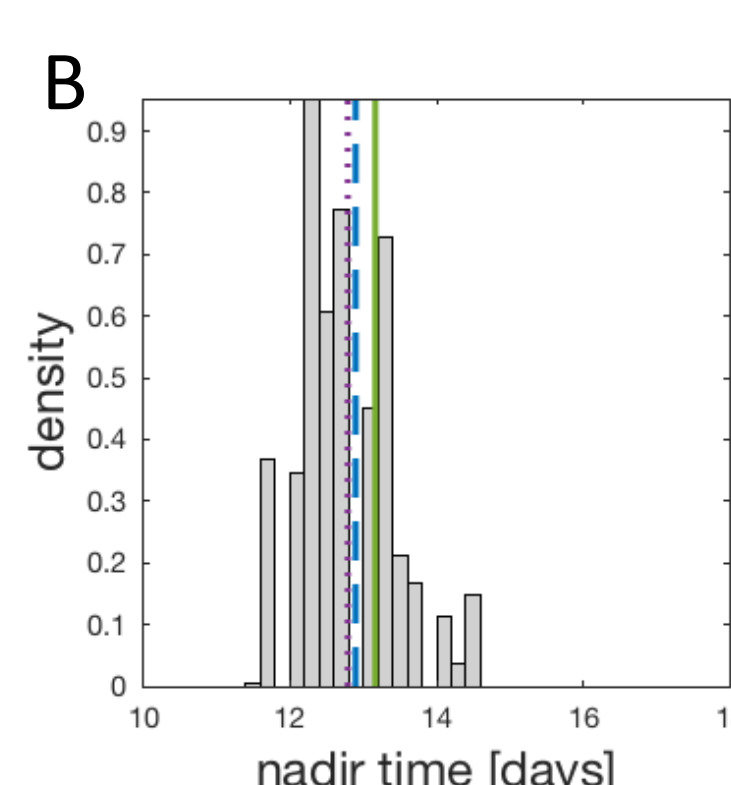
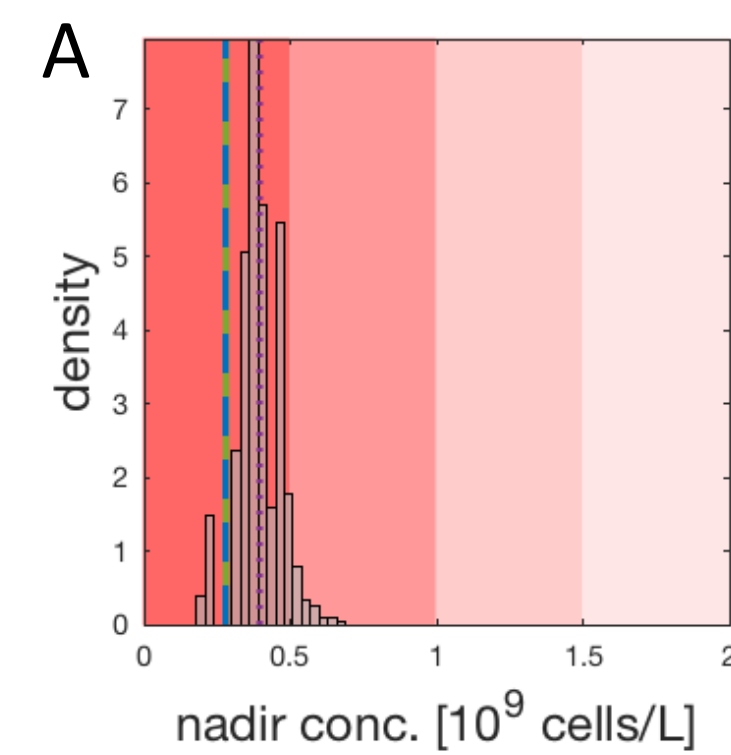
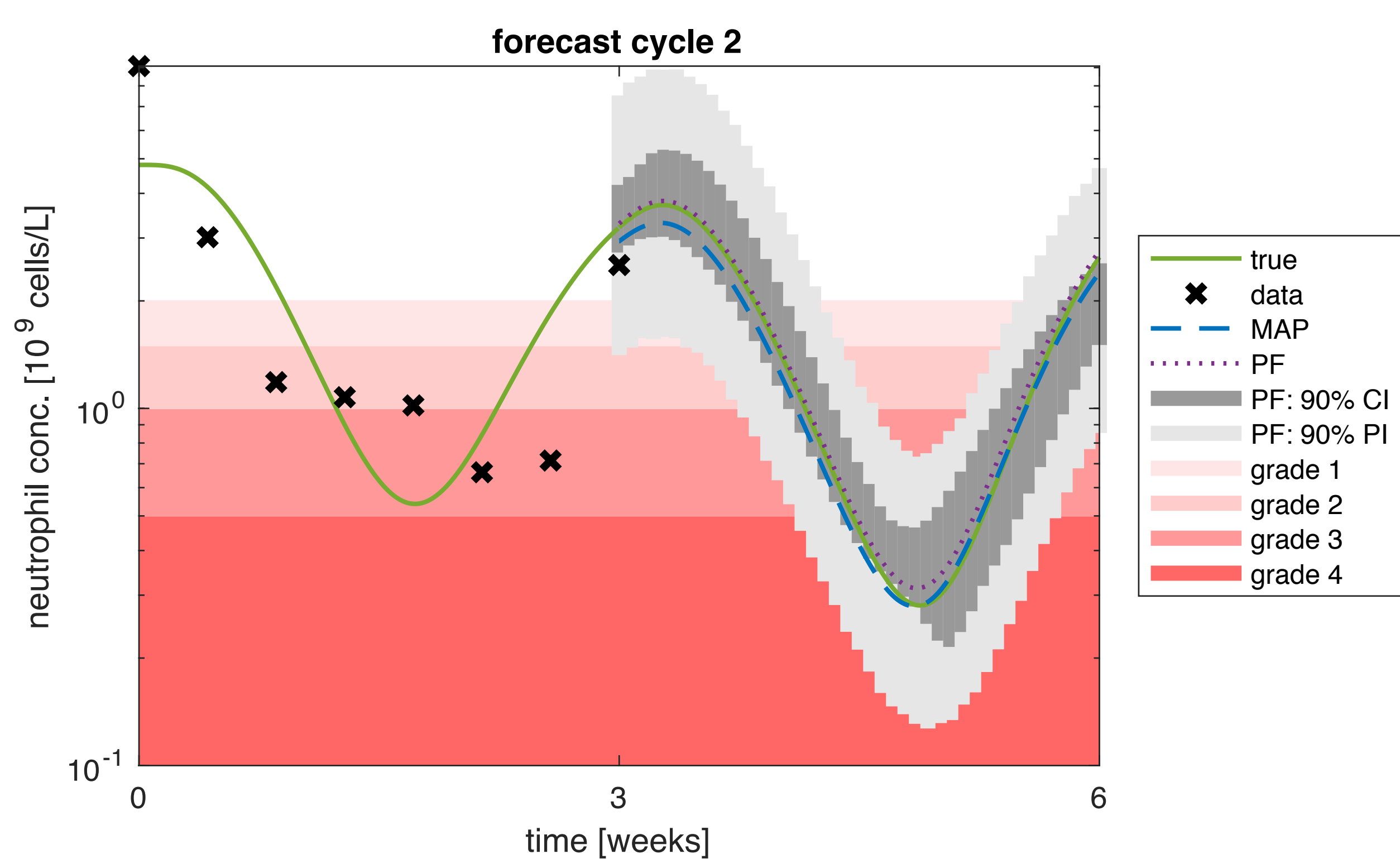
- Estimation of the mode of the posterior
- $$\hat{\theta}^{\text{MAP}} = \arg \min_{\theta^{\text{ind}}} \sum_{i=1}^{n_{\text{data}}} \frac{(y_i^{\text{obs}} - y_i^{\text{pred}}(\theta^{\text{ind}}))^2}{\sigma^2} + \sum_{k=1}^{n_{\text{par}}} \frac{(\log(\theta_k^{\text{TV}}) - \log(\theta_k^{\text{ind}}))^2}{\omega_k^2}$$
 for lognormal IIV model and log-transformed data.
- Applied by Netterberg et al. [5] for single cycle
- Drawbacks:
 - Point estimate without information on uncertainty
 - Possibly only local optimum
 - Complete re-estimation necessary whenever new data points become available

Simulation study of multiple cycle therapy

- Paclitaxel (185 mg/m², 3h i.v. infusion), every 3 weeks for 6 cycles
- Simulated data: every third day with additive error on log-scale
- Virtual Population based on CEPAC-TDM study [3] population
- Bone marrow exhaustion model [2] for neutropenia with IOV on PK parameters

- 1000 particles per virtual patient
- Results displayed for resampling + rejuvenation
- Similar results with transformation algorithms, however, higher RMSE in parameter estimates

Results



A Uncertainty quantification for nadir conc.
→ Risk assessment based on current knowledge and detection of suboptimal treatment

B Time until lowest neutrophil conc.
→ Time management for intervention

C Probability of grade 4 and time until grade 4
→ Identify patients at risk and adapt dose individually, e.g. such that P[grade 4]=1%

D Probability to reach grade 0 within cycle length (21 days) and time until neutrophil count $\geq 1.5 \cdot 10^9$ cells/L
→ Predict recovery to schedule the next cycle individually

Conclusion:

- Efficient computation of decision statistics via recursive patient data processing
 - Comparable forecast RMSEs to MAP estimation
 - Comprehensive uncertainty quantification in contrast to prior work [5]
 - Easy-to-interpret results allow to rate the predicted individual treatment outcome
- Support for rational and individual decision-making in oncology

Open research questions:

- Currently: “best-case-scenario” as data is simulated with the model
- Adapt transform algorithms for improved parameter estimation
- Learning with every patient: update prior knowledge for next patient with posterior of current patient → hierarchical Bayes

References:

- [1] www.philips.co.uk/healthcare/education-resources/publications/hotspot/minicare-home
[2] Henrich et al. J Pharmacol Exp Ther. 2017
[3] Joerger et al. Ann Oncol. 2016
[4] Reich and Cotter, Cambridge University Press, 2015
[5] Netterberg et al. Cancer Chemother Pharmacol. 2017

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