



Predicting the absolute neutrophil count with frequent measurements during docetaxel-induced myelosuppression

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Ida Netterberg, Lena E Friberg, Elisabet I Nielsen, Mats O Karlsson
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Introduction

Consequences of limited absolute neutrophil count (ANC) monitoring during chemotherapy-induced myelosuppression may include (i) patients experiencing life-threatening conditions, (ii) inconvenience for the patient and the clinic if the next cycle needs to be delayed due to low ANC and (iii) cautious dosing. Technological advances may make daily ANC monitoring in home-labs possible in the near future.

Objective

This study aim to investigate how frequent monitoring of the ANC, together with model-based analysis and prediction, could improve therapy.

Methods

1. Simulations of the ANC

- Model: Myelosuppression model by Friberg *et al.* [1] (Figure 1) and parameter estimates according to Kloft *et al.* [2]
- Schedule: At baseline and thereafter daily from day 3 to 21 (no simulations at day 1 and 2)
- Patients: 601 (=N) patients administered a 1-hour infusion of 75 or 100 mg/m² docetaxel [3]

2. Predictions of the ANC at each day of the cycle

- Scenarios: Varying sampling duration and frequency, an example of a scenario is illustrated in Figure 2
- Characteristics: Time to baseline (TBA), time to nadir (TNADIR) and ANC value at nadir (VNADIR)

3. Evaluation

- Root-mean square error (RMSE): Predicted individual characteristics ($Char_{pred,i}$) compared to the respective characteristic computed from the true individual profile ($Char_{true,i}$) (Eq. 1)
- Relative estimated error (REE_i): Comparing the predicted individual ANC ($ANC_{pred,i}$) and the true individual ANC ($ANC_{true,i}$) (Eq. 2)

$$RMSE = \sqrt{\frac{\sum_{i=1}^N (Char_{pred,i} - Char_{true,i})^2}{N}} \quad (1) \quad REE_i = \frac{ANC_{pred,i} - ANC_{true,i}}{ANC_{true,i}} \quad (2)$$

The analysis was carried out using NONMEM 7.2 [4]

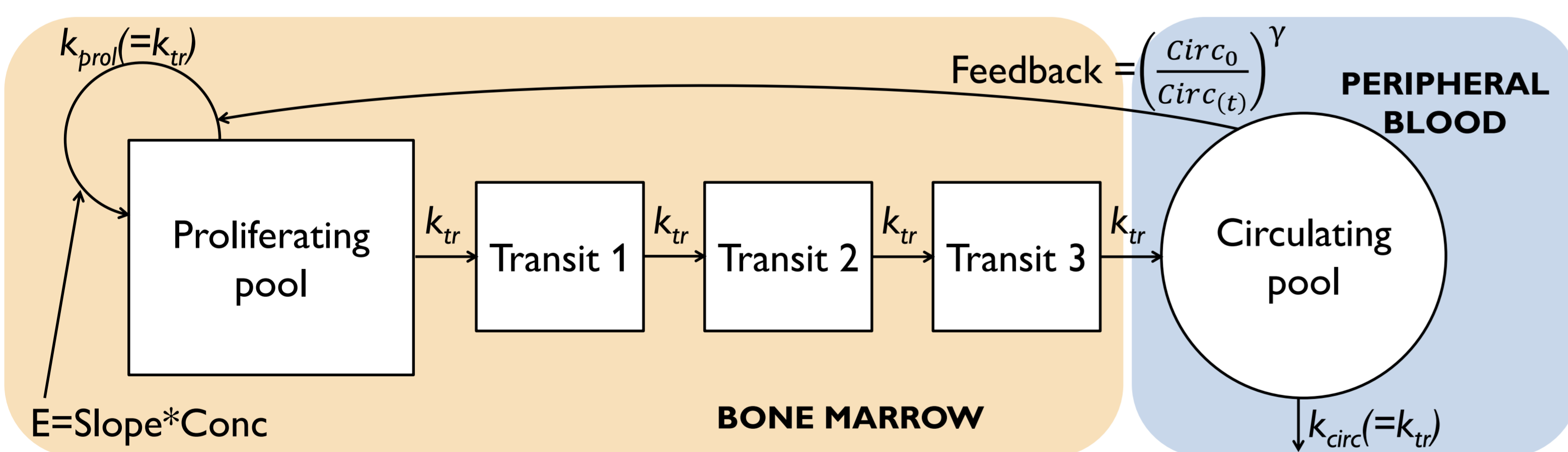


Figure 1. The myelosuppression model by Friberg *et al.* $Circ_0$ is the ANC at $t=0$ and $Circ(t)$ is the ANC at $t=t$. E is the chemotherapeutic drug effect.

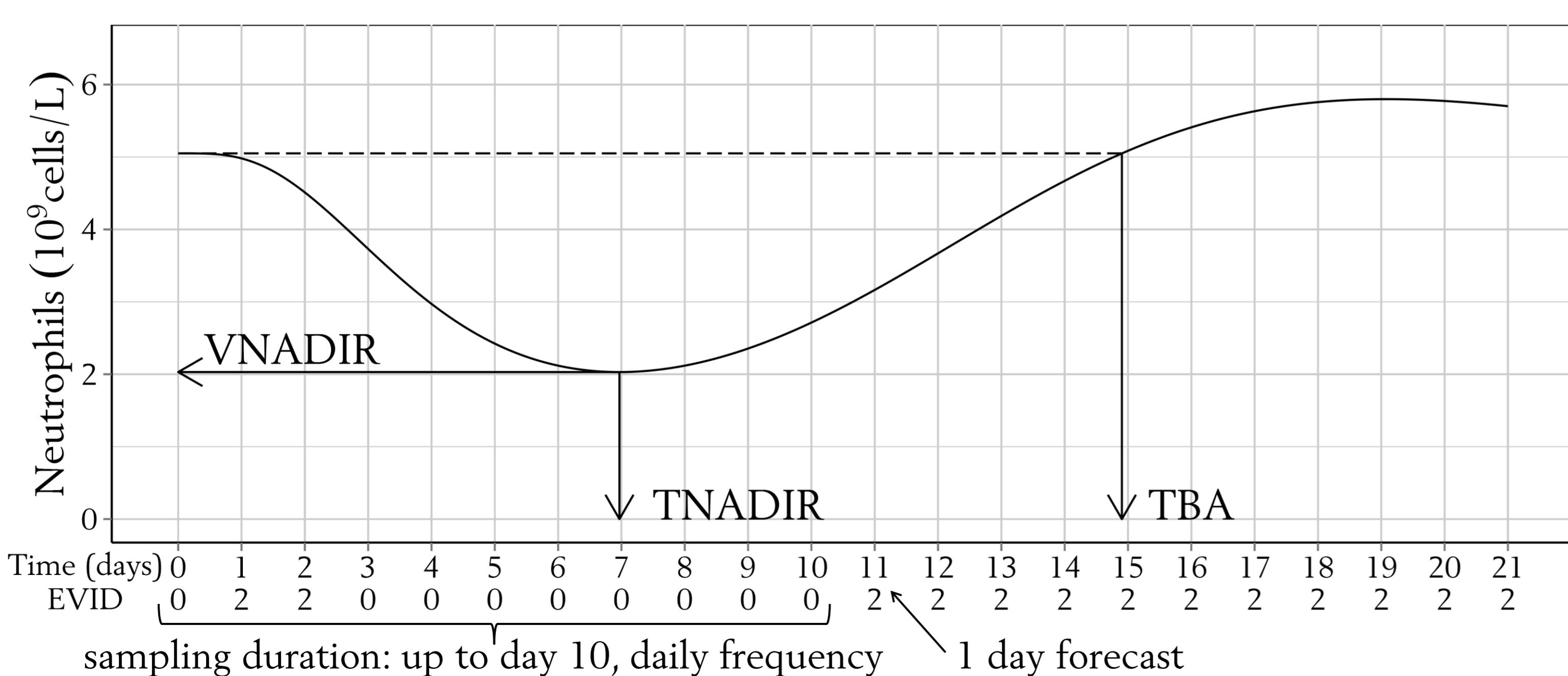


Figure 2. The myelosuppression time-course, marked with the characteristics evaluated in this study. EVID is the NONMEM variable event ID (0=observation and 2=other). In this example daily ANC were sampled up to 10 days and a one day forecast was done.

Results

1. RMSE (Fig. 3)

- Scenarios: More frequent sampling schedule, less imprecision
 - TBA: Approximately 15 days
 - TNADIR: Approximately 15 days
 - VNADIR: Approximately 12 days
- No improvement in imprecision with longer sampling duration
- RMSE of VNADIR: Decreased from 0.439 (805 %) to 0.303 (346 %) 10^9 cells/L with an ANC measurement only at baseline and data at baseline and daily from day 3 to 6, respectively.

2. REE (Fig. 4)

- Scenarios: Longer forecasts, increased range of the REE
- Around nadir (i.e. day 7 for docetaxel): More bias in the 1 day forecast compared to earlier and later in the cycle

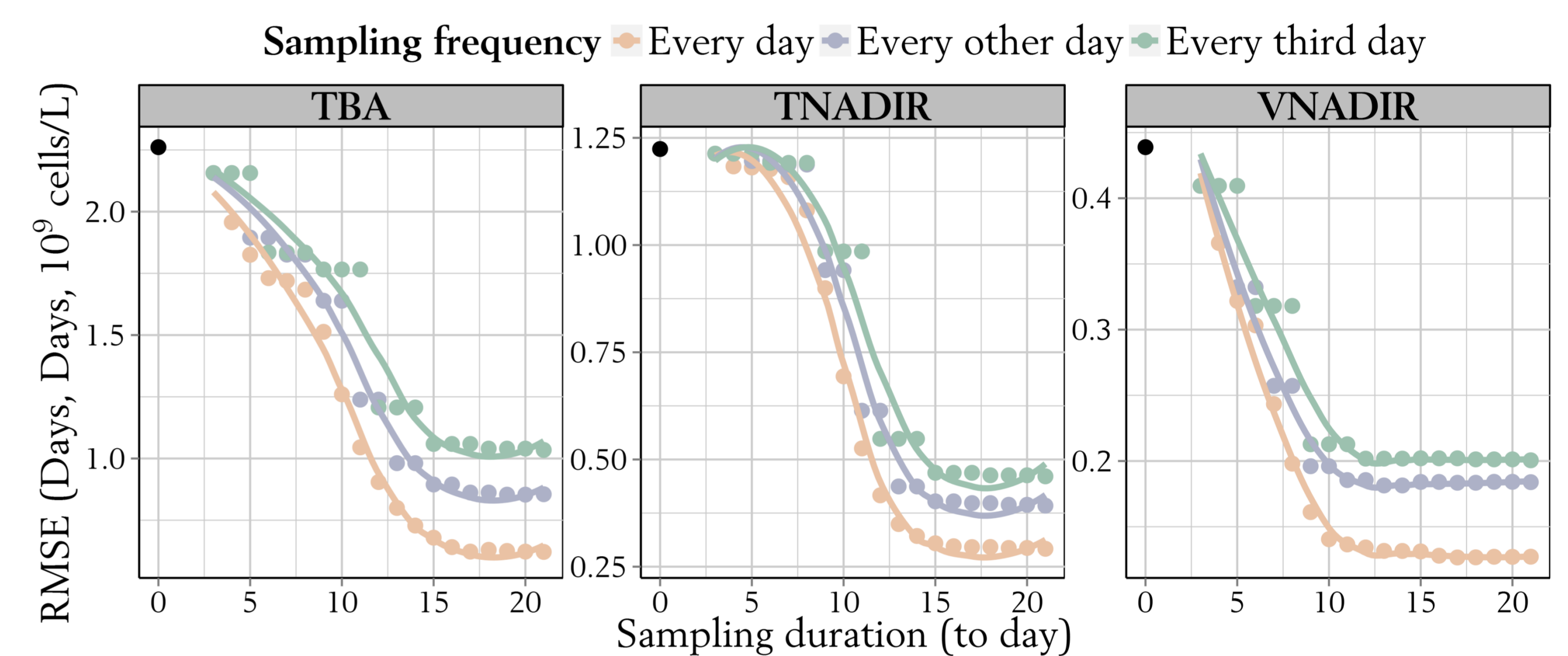


Figure 3. RMSE of TBA, TNADIR and VNADIR in the different scenarios. Solid lines are smooth through the computed RMSE dots. The black dots are RMSE computed with data only at baseline.

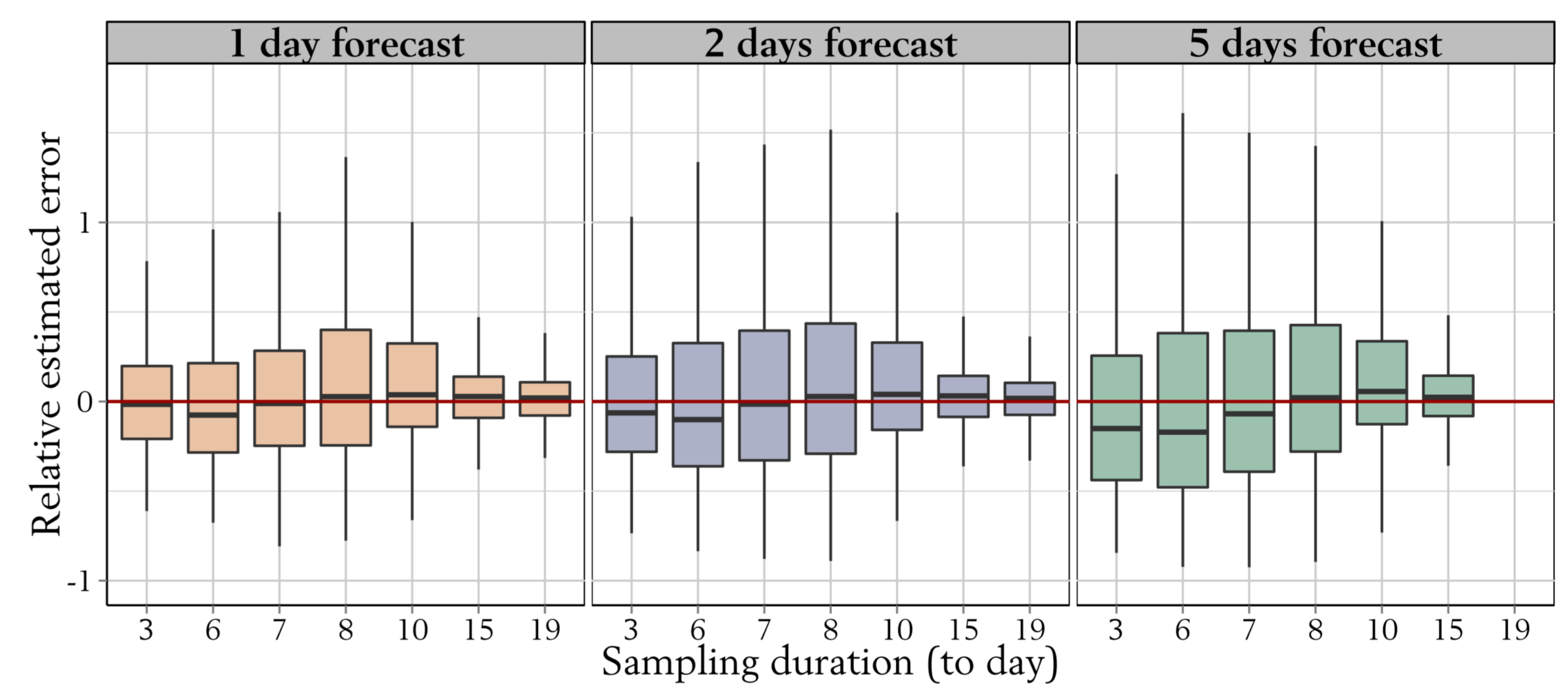


Figure 4. The impact on the REE depending on the sampling duration and length of the forecasts. Upper and lower hinges of the box represent the 75th and 25th percentile respectively. The vertical black line of the box is the median. Upper and lower ends of the whiskers corresponds to the 75th percentile + 1.5*IQR and 25th percentile - 1.5*IQR respectively, IQR is the interquartile range. The horizontal solid red line represent a REE of 0, i.e., True ANC = Predicted ANC. No outliers are shown.

Conclusions

Increased number of measurements of ANC together with model predictions could improve therapy with respect to patient safety, e.g. predicting nadir early in the cycle, and convenience for the patient and the clinic, i.e. reschedule the start of the next cycle.

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References

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- [3] R. Bruno *et al.*, *J Pharmacokinetics Biopharm*, 1996, pp. 153-172
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