

Mathematical model of the Human Inflammatory Response to Acute and Prolonged Lipopolysaccharide Exposure

Freek Relouw^{1,2,3,4,5}, Matthijs Kox¹, Rob Taal², Birgit Koch³, Menno Prins^{4,5,6} and Natal van Riel^{4,5}

¹Dept. of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, NL
²Dept. of Pediatrics, Division Neonatology, Erasmus MC, University Medical Center-Sophia Children's Hospital, Rotterdam, NL
³Dept. of Hospital Pharmacy, Erasmus MC, University Medical Center, Rotterdam, NL
⁴Dept. of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, NL
⁵Institute of Complex Molecular Systems, Eindhoven University of Technology, Eindhoven, NL
⁶Dept of Applied Physics, Eindhoven University of Technology, Eindhoven, NL

CONTACT INFORMATION:
f.j.a.relouw@tue.nl
n.a.w.v.riel@tue.nl

INTRODUCTION

- Cytokines play a pivotal role in the immune response during sepsis [1]:
 - Dynamically changing over hours to days in critically ill patients on the ICU
 - Interleukin-6 (IL-6) inhibits drug metabolizing enzymes [2]
- The Human endotoxemia model:
 - An *in vivo* method to study the dynamics of the inflammatory response [3]
 - Healthy human subjects receive a dose of lipopolysaccharide (LPS)
 - Typically, short timescales of several hours
- In silico* models to bridge the gap between human endotoxemia and infections:
 - Current model limited due to oscillations on longer timescales [4]
 - Current model cannot accurately capture the LPS dose-response [5]

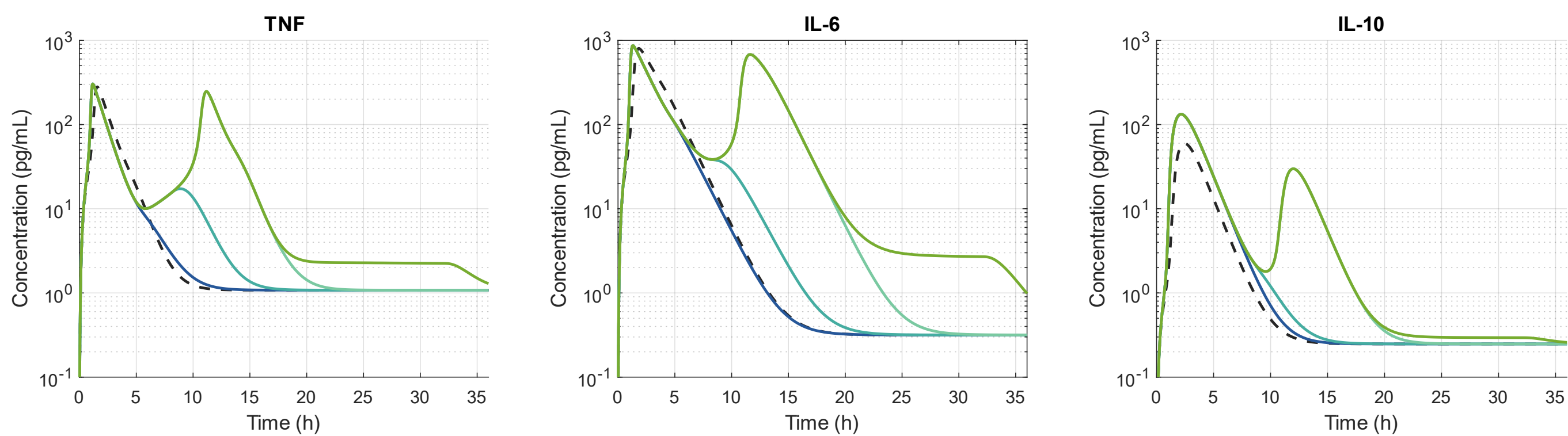


Fig. 1: Extrapolation of model by Dobрева et al. (2021). Model prediction to LPS bolus (black dotted) and sustained LPS concentrations for 4, 8, 16, and 32 hours. Model starts to oscillate on longer timescales.

OBJECTIVES

- Develop a multiscale **Ordinary Differential Equation (ODE) model** of the **inflammatory response** observed during human endotoxemia
- Use the model to **bridge the timescales** between human endotoxemia and clinical infections

MODEL

- The ODE model exists of 15 equations and 48 parameters
- Half the parameters were estimated from literature dose-response curves
- Other parameters were estimated using calibration data of 1 ng/kg [6]

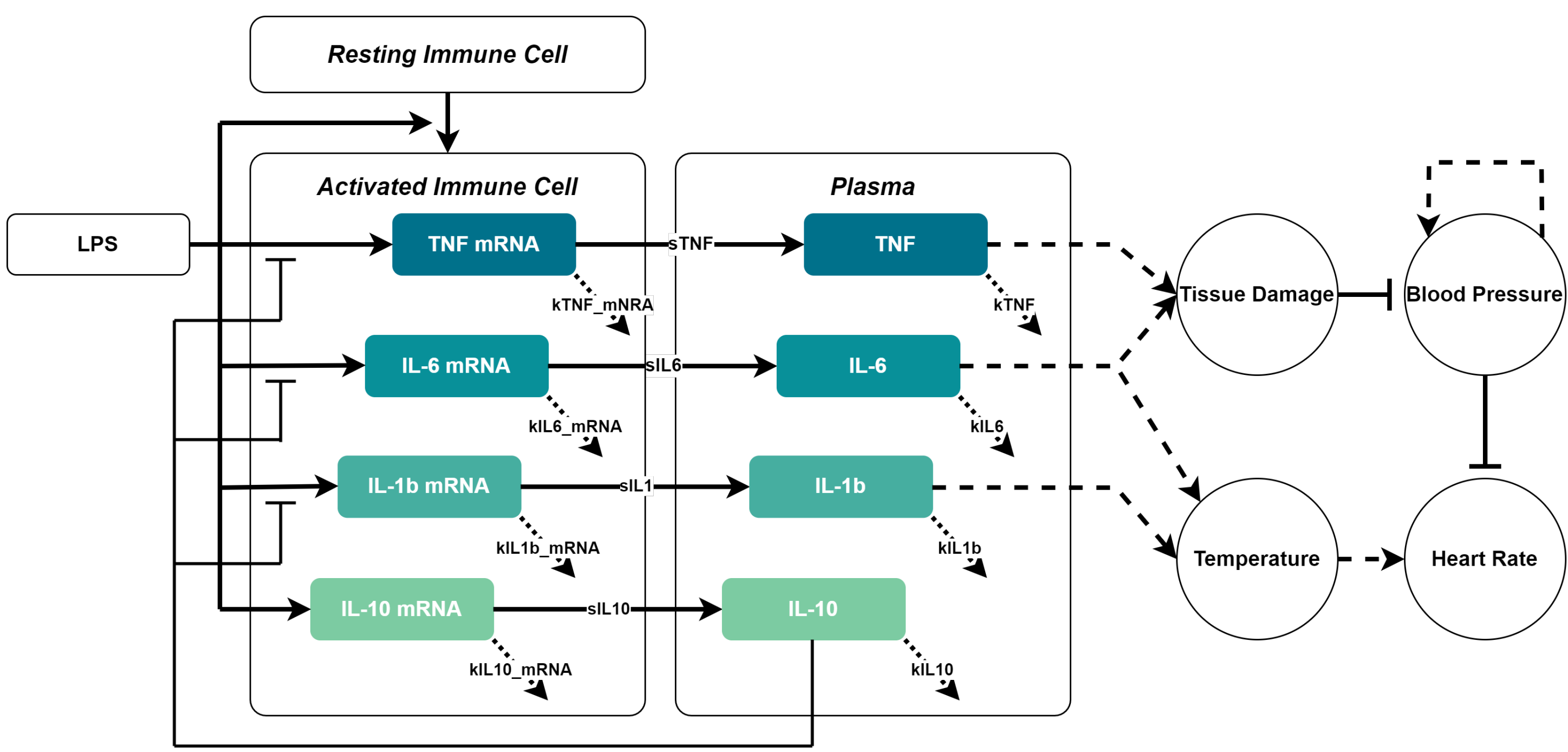


Fig. 2: Structure of the ODE model. LPS is used as an input to the model, activating immune cells. These activated immune cells start producing pro- and anti-inflammatory cytokines. These cytokines influence the macro-scale variables such as temperature, heart rate, and blood pressure.

METHODS

- Dose-response data from *in vitro* experiments were used for parameterization
- Calibration and Validation based on data from *in vivo* human endotoxemia:
 - 0.3, 0.5, 1, and 2 ng/kg bolus LPS and 1 ng/kg/h LPS infusion [6] [7] [8]
- Parameter sensitivity and local identifiability were assessed

RESULTS

- A subset of six sensitive parameters are selected for (re-)estimation
- Parameters are locally identifiable
- Model accurately predicts:
 - Response to LPS dose-response
 - Response to LPS infusion
 - Observed cytokine concentrations compared to vitals in sepsis patients

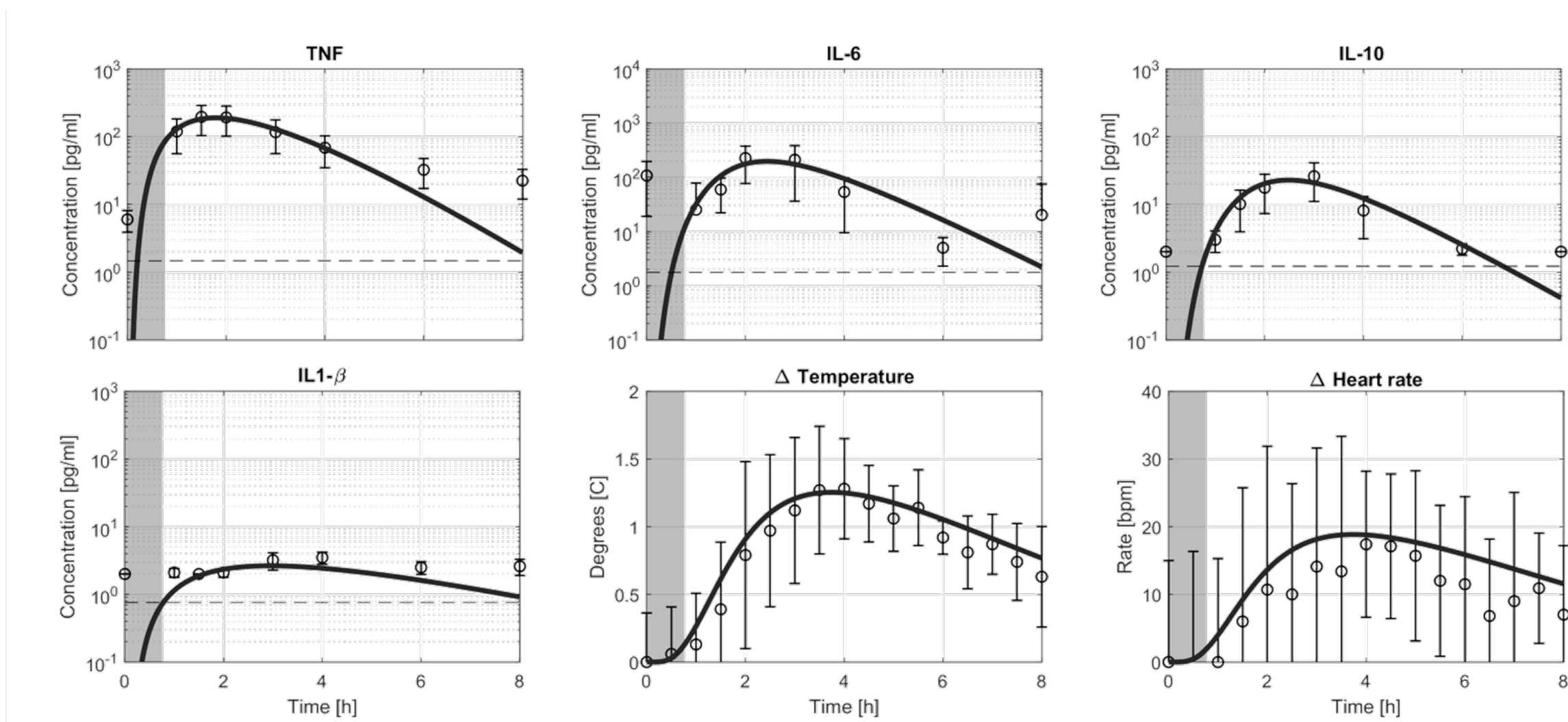


Fig. 3: Model fit to the calibration data of 1 ng/kg [6]. The predicted concentration times and peaks match with the data. Individual artifacts in the data of the last time point of the cytokine data cause discrepancies.

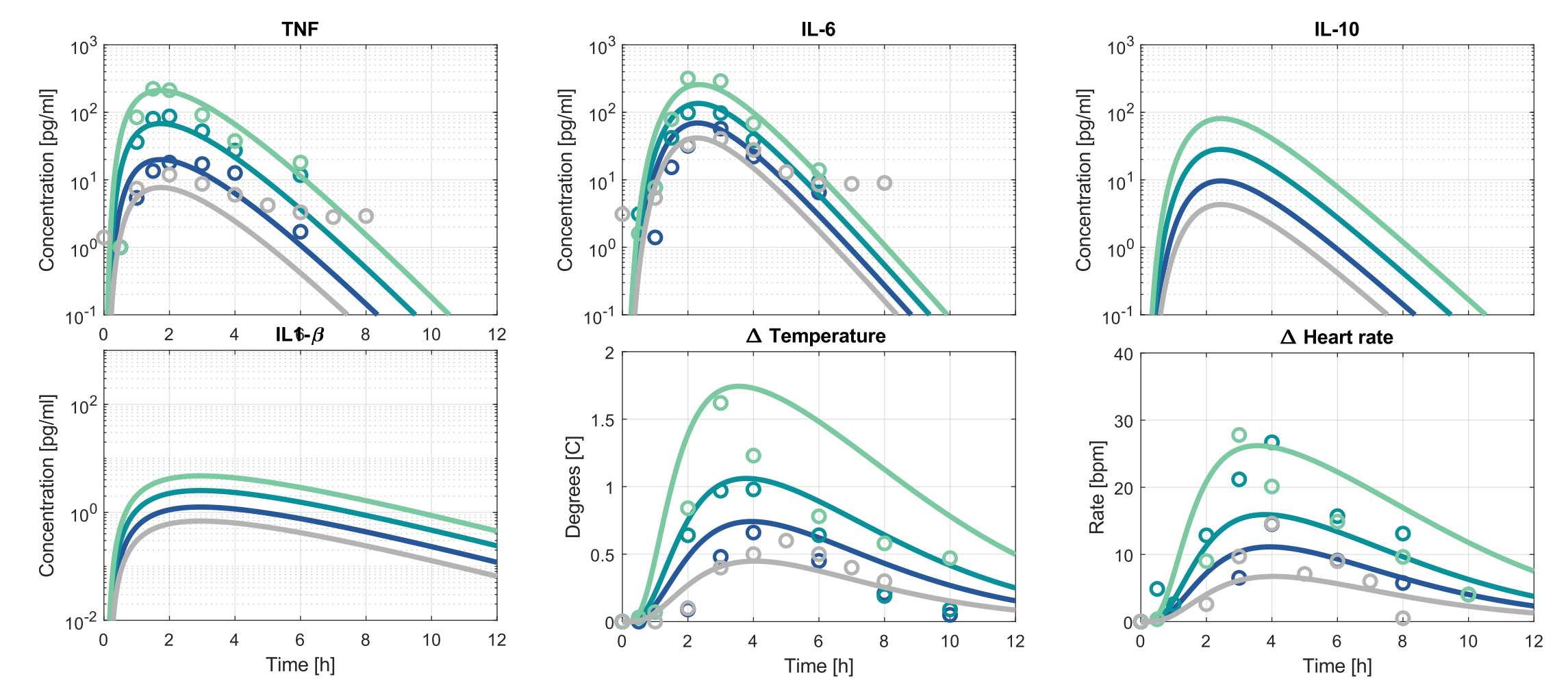


Fig. 4: Model prediction with the dose-response validation data. From bottom to top, response to 0.3, 0.5, 1, and 2 ng/kg LPS bolus [7] [8]. Prediction of temperature and heart rate changes take longer to return to baseline compared to experimental data.

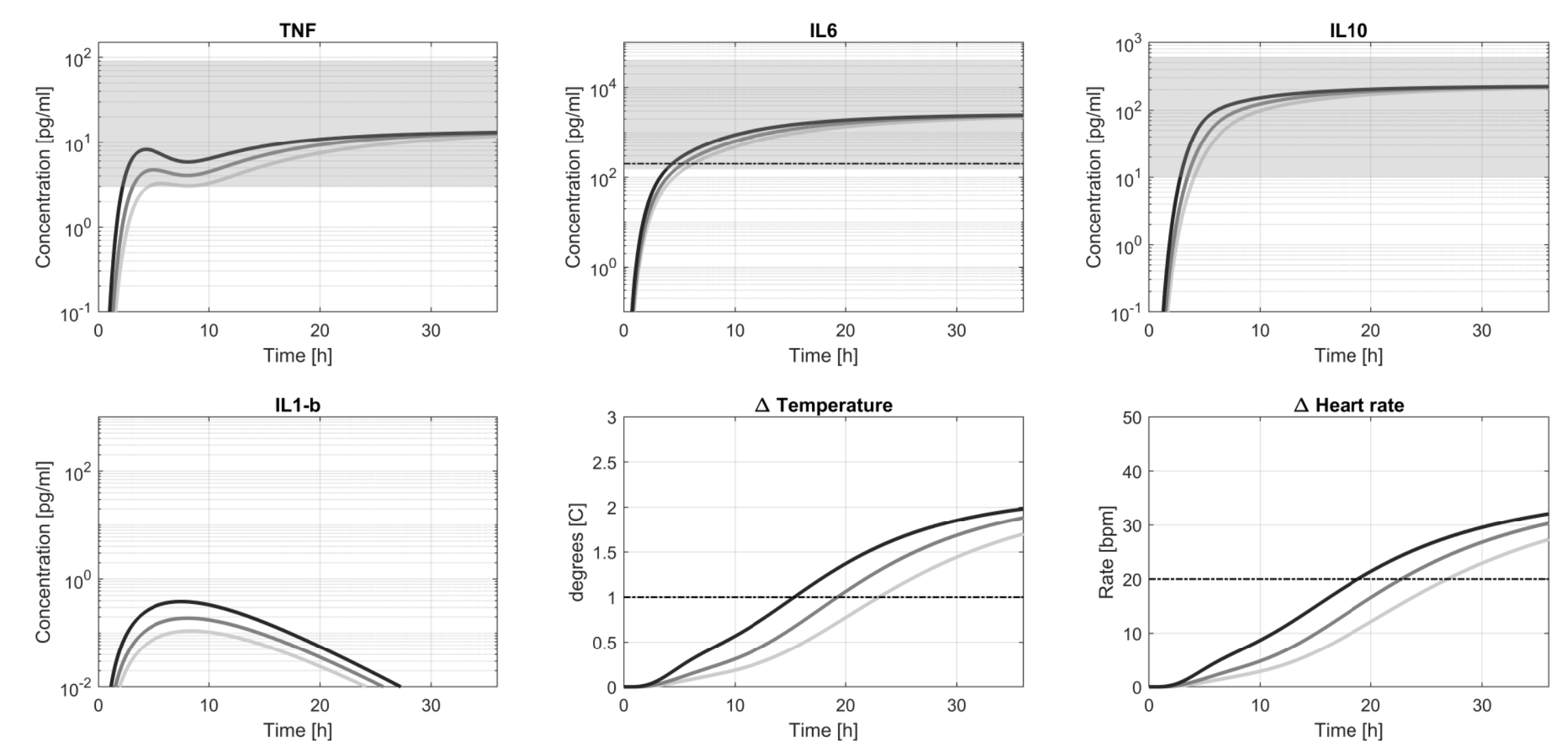


Fig. 5: Model extrapolation to long timescales. Infection was modeled by giving an asymptotically shaped LPS profile as input with varying slopes to simulate an infection. Gray area represents clinically observed cytokine concentrations.

CONCLUSIONS

- This work presents a first step towards an **inflammation simulation model**
- Model could be extended with **more intricate pathways** in the future
- Future extensions could also incorporate **kidney and liver function dynamics** during clinical infections [9]
- Has the potential to be used in a **QSP framework** to investigate inflammation and drug interactions in a dynamic way

REFERENCES

[1] Zhang et al. *Intern. Anesth. Clinics* vol. 45 27–37 (2007).
[2] Harvey et al. *Clin. Pharm. & Ther.* vol. 96 449–457 (2014).
[3] van Lier et al. *Biochimie* vol. 159 99–106 (2019).
[4] Dobрева et al. *The Journal of Physio.* vol. 599 1459–1485 (2021).
[5] Windolowski et al. *Experimental Physiology* (2024).
[6] Kiers et al. *Sci Rep* 7, 40149 (2017).
[7] Taudorf et al. *Clin Vaccine Immunol* 14, 250–255 (2007).
[8] Dillingh et al. *Journal of Inflammation* 11, 28 (2014).
[9] Liu et al. *Euro. Journal of Drug Meta. and PK* vol. 48 623–631 (2023).

LINKEDIN



PREPRINT

