

Systems biology model of the mucosal immune system in the context of IBD

Sabine Stübler^{1,2}, Charlotte Kloft³, Wilhelm Huisinga^{2,4}

¹PharMetriX Graduate Research Training Program: Pharmacometrics & Computational Disease Modelling, Freie Universität Berlin/Universität Potsdam, ²Institut für Biochemie und Biologie, Universität Potsdam, ³Institut für Pharmazie, Freie Universität Berlin, ⁴Institut für Mathematik, Universität Potsdam

Inflammatory bowel disease (IBD) & treatment

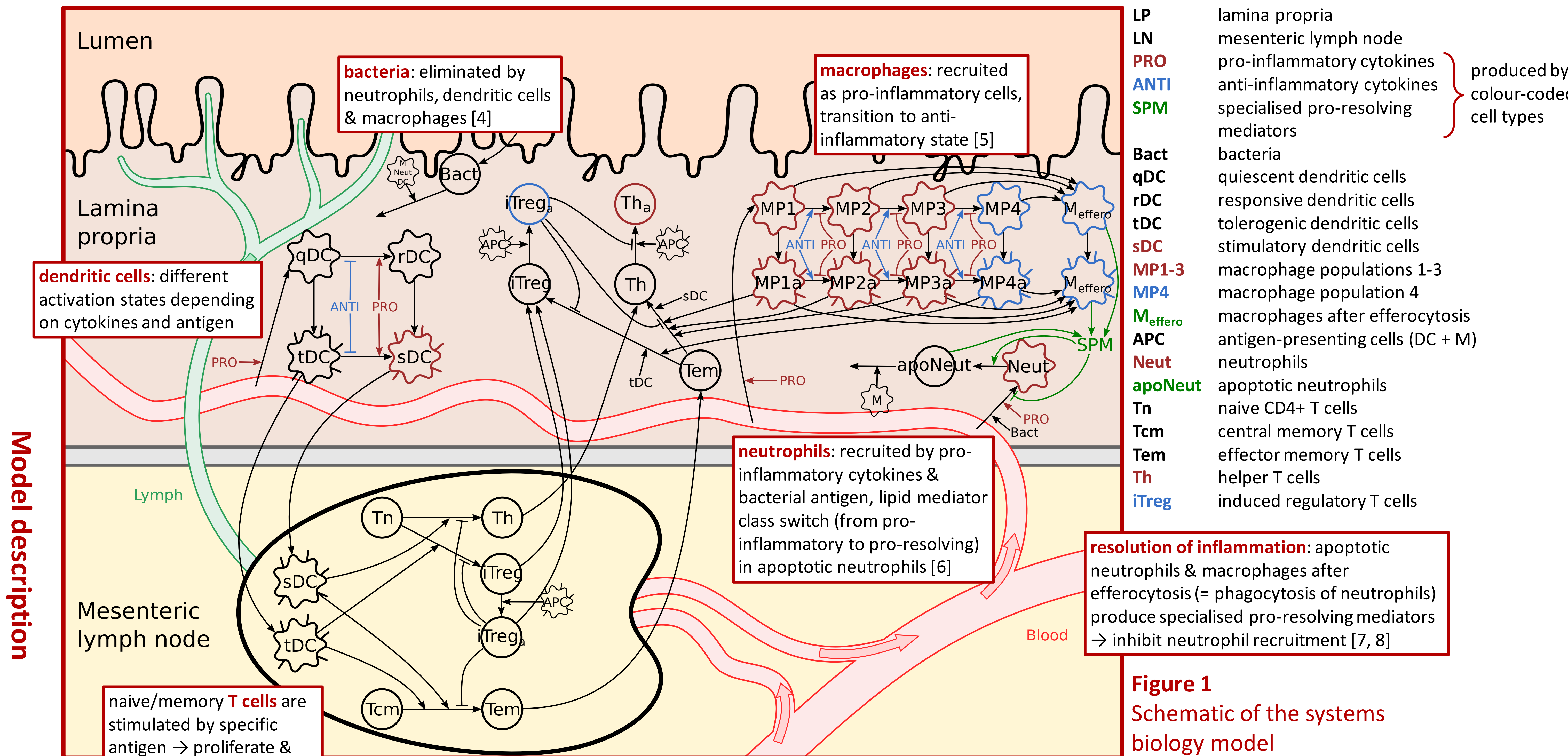
IBD (Crohn's Disease & Ulcerative Colitis) is characterised by a chronic inflammation in the gastrointestinal tract. Treatment strategies include anti-inflammatory and immunosuppressive drugs and **monoclonal antibodies (mAb)** against the cytokine **TNF- α** [1]. The therapeutic outcome of the different therapies is **highly variable** between patients [2].

Objectives

Our aim is to understand the underlying mechanisms for the high variability in therapeutic outcome. We propose to use a systems biology approach, **modelling the cellular processes** of the mucosal immune system in IBD and the effects of various treatments. As a starting point we used the 'model of colonic inflammation' by Wendelsdorf et al. [3].

Methods

We developed a systems biology model of **ordinary differential equations**, describing the concentrations of **various cell types of the mucosal immune system** in healthy steady state and infection. Parameters are based on **literature search** (human studies, if available, but also murine and in vitro studies). The results are intended **qualitative rather than quantitative**.



Open questions

Role of B cells and antibodies

- B cell proliferation with T cell help in lymph node (LN)
- production of pathogen-specific antibodies binding to bacteria, increasing elimination of bacteria
- relevance in IBD?

Bacteria dynamics

- differences commensal/pathogenic bacteria?
- survival/proliferation of bacteria in mucus layer and lamina propria (LP)?

Tissue destruction

- integrity of the epithelial barrier
- cause and effects of epithelial destruction in infection and IBD
- marker for disease severity [9]?

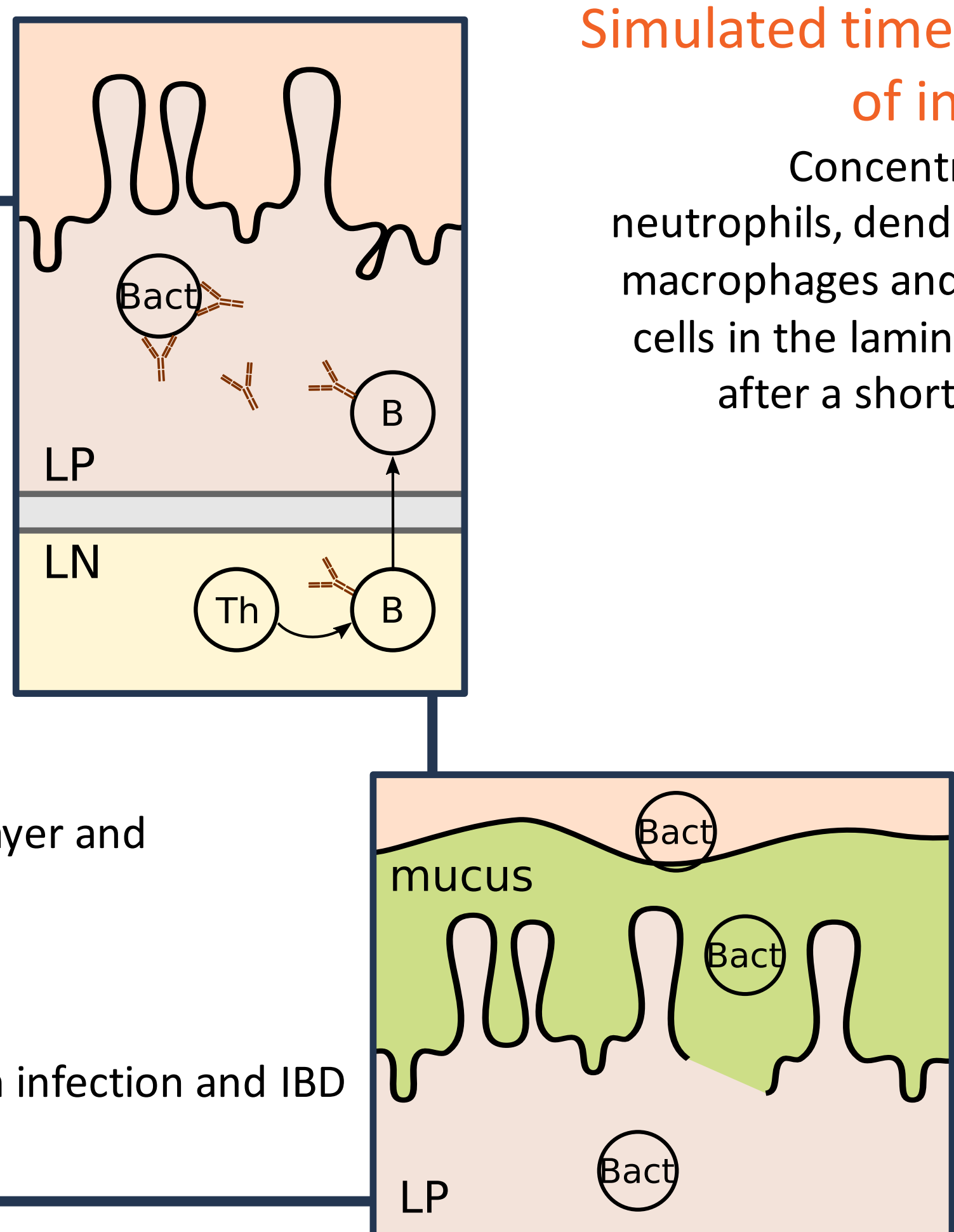
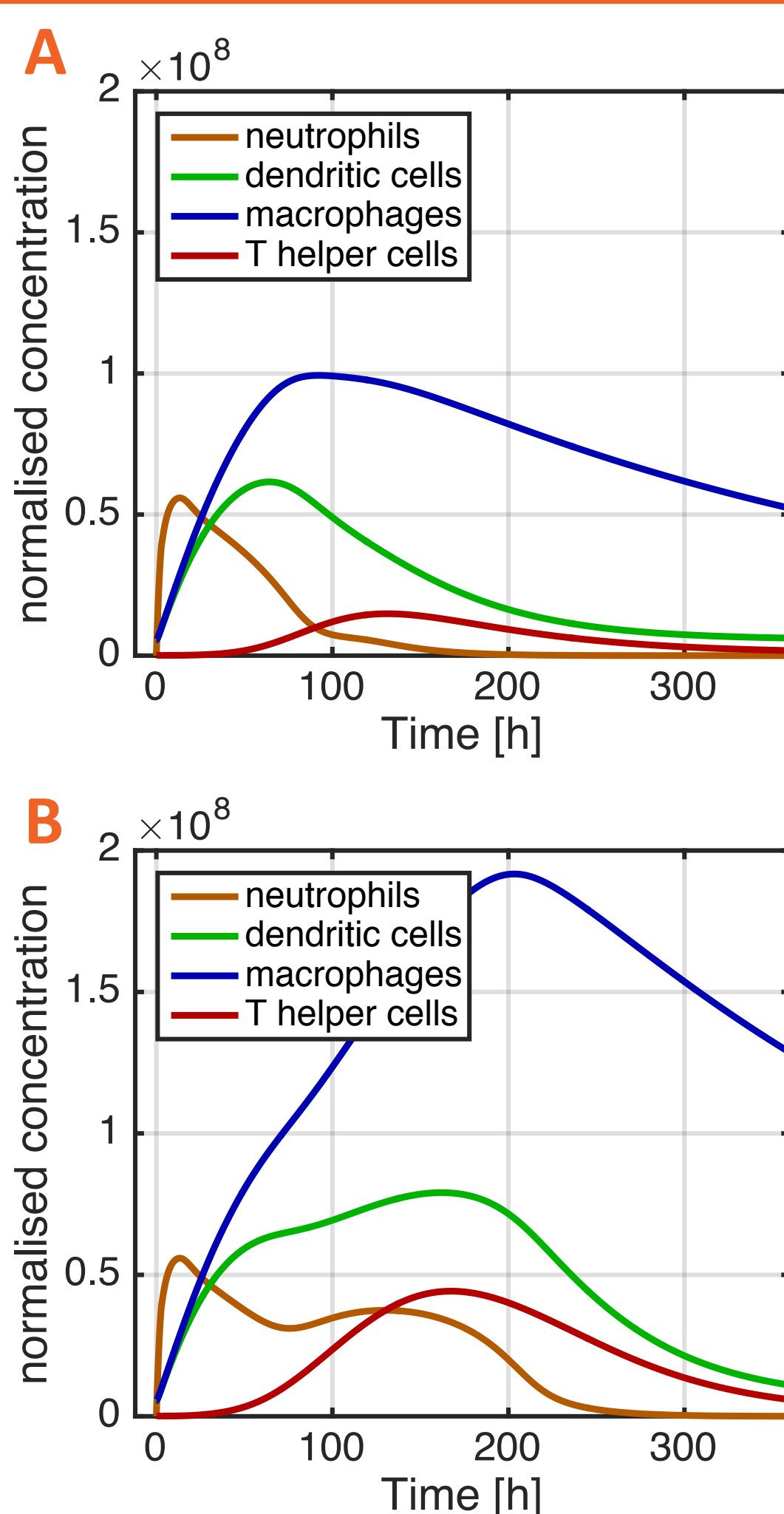


Figure 2
Simulated time course of infection

Concentrations of neutrophils, dendritic cells, macrophages and T helper cells in the lamina propria after a short bacterial stimulus



A Primary infection

- fast increase of neutrophil conc.
- recruitment of macrophages and dendritic cells by neutrophils
- stimulation of naive T cell proliferation by dendritic cells
- as comparison: the shape of neutrophil and macrophage concentrations mirrors the murine peritonitis model in [10,11]

B Secondary infection

- memory T cells specific for pathogenic antigen available
- larger concentration of T helper cells
- T helper cells increase recruitment and inhibit apoptosis of neutrophils
- higher number of neutrophils recruit higher numbers of macrophages and dendritic cells

Simulation results

Future directions

IBD

For simulation of IBD, (combinations of) parameters will be altered to find changes leading to **chronic inflammation**. The resulting parameters important for IBD pathophysiology will be compared to published **changes in IBD** and **genetic polymorphisms** related to IBD (e.g. [12]).

Treatment

To simulate treatment of IBD, we need to account for the PK and the **different drug effects** (anti-TNF- α , corticosteroids,...). For this, we will link the systems biology model to a **PK model** and account specifically for the drug targets (e.g. TNF- α and binding the mAbs).

Variability

A **virtual population of IBD patients** with inter-individual variability will help to define which parameters have the largest **effects on disease and responsiveness to treatment**.

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