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Inflammatory bowel diseases (IBD)

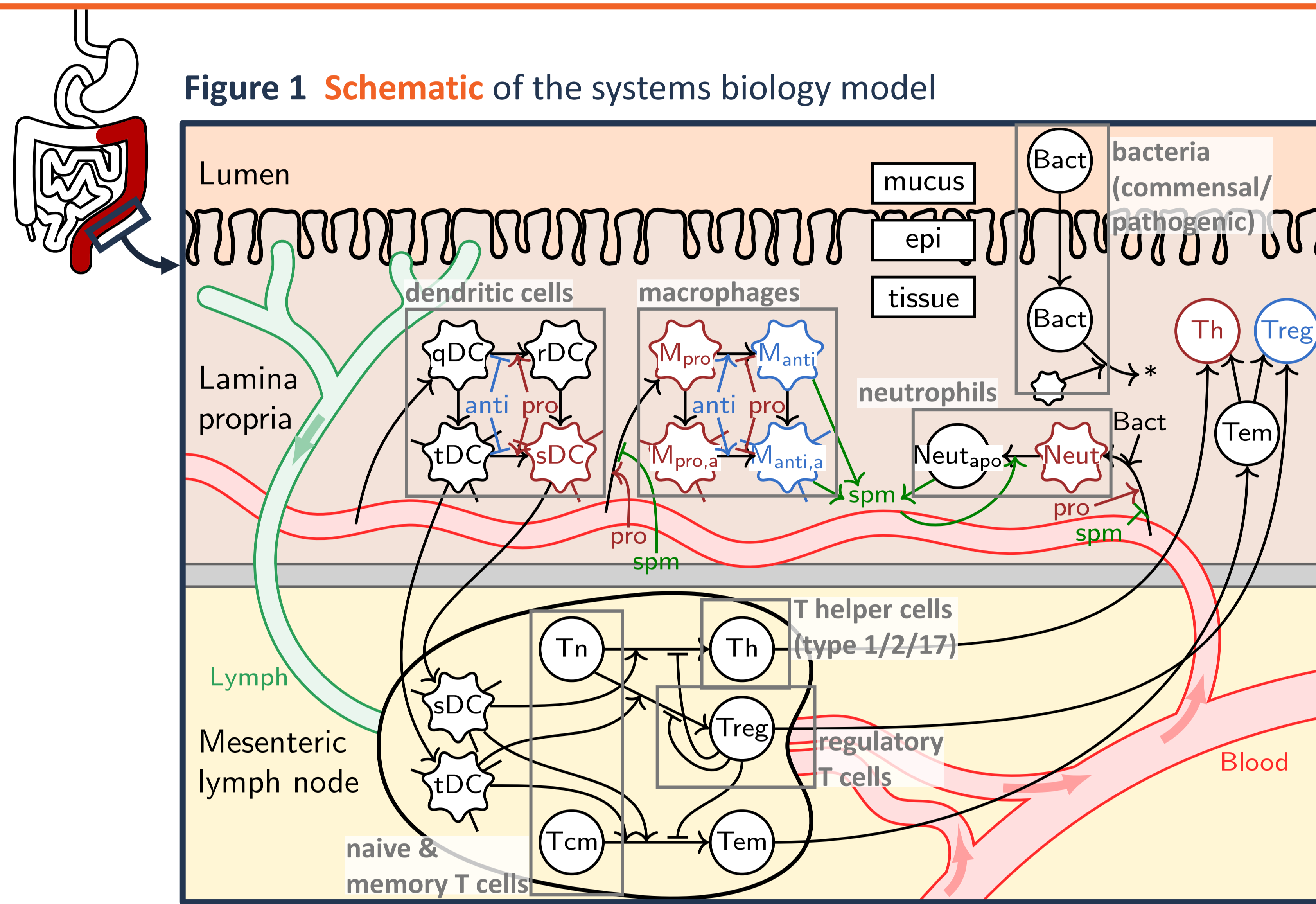
IBD (Crohn's Disease & Ulcerative Colitis) are characterised by a **chronic inflammation** in the gastrointestinal tract. The pathogenesis has not been fully elucidated, but many **genetic dispositions** and **environmental stimuli** have been associated with the disease. IBD arises as result of a combination of different triggers.

Treatment

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]. A better understanding of the underlying mechanisms for this high variability is highly desirable.

Objectives

We aim at analysing the **influence of specific processes and cell types on the treatment outcome**, using a systems biology approach. As basis for simulation of chronic inflammation and treatment thereof, a model describing the **healthy mucosal immune system** is developed.



Methods

Based on **literature data**, we developed a systems biology model of **ordinary differential equations**, describing the rate of change of the concentrations of **various cell types** of the healthy mucosal immune system challenged by commensal and pathogenic bacteria. The results are intended to give a **qualitative insight rather than a quantitative one**.

Abbreviations

- pro/anti** pro-/anti-inflammatory cytokines (produced by colour-coded cell types)
- spm** specialised pro-resolving mediators
- Bact** bacteria
- (q/r/t/s)DC** quiescent/responsive/tolerogenic/stimulatory dendritic cells
- M_{pro}/M_{anti}** pro-/anti-inflammatory macrophages
- Neut_(apo)** (apoptotic) neutrophils
- Tn** naive CD4+ T cells
- Tcm/Tem** central/effector memory T cells
- Th** T helper cells
- Treg** regulatory T cells
- phagocytic cells**
- antigen-presenting cells (DC & M)**

Simulation

Analysis

Figure 2 Simulation of acute inflammation scenarios as qualitative check of model behaviour

Concentrations of bacteria and immune cells in lamina propria over time. The time courses qualitatively reflect expectations gained from literature.

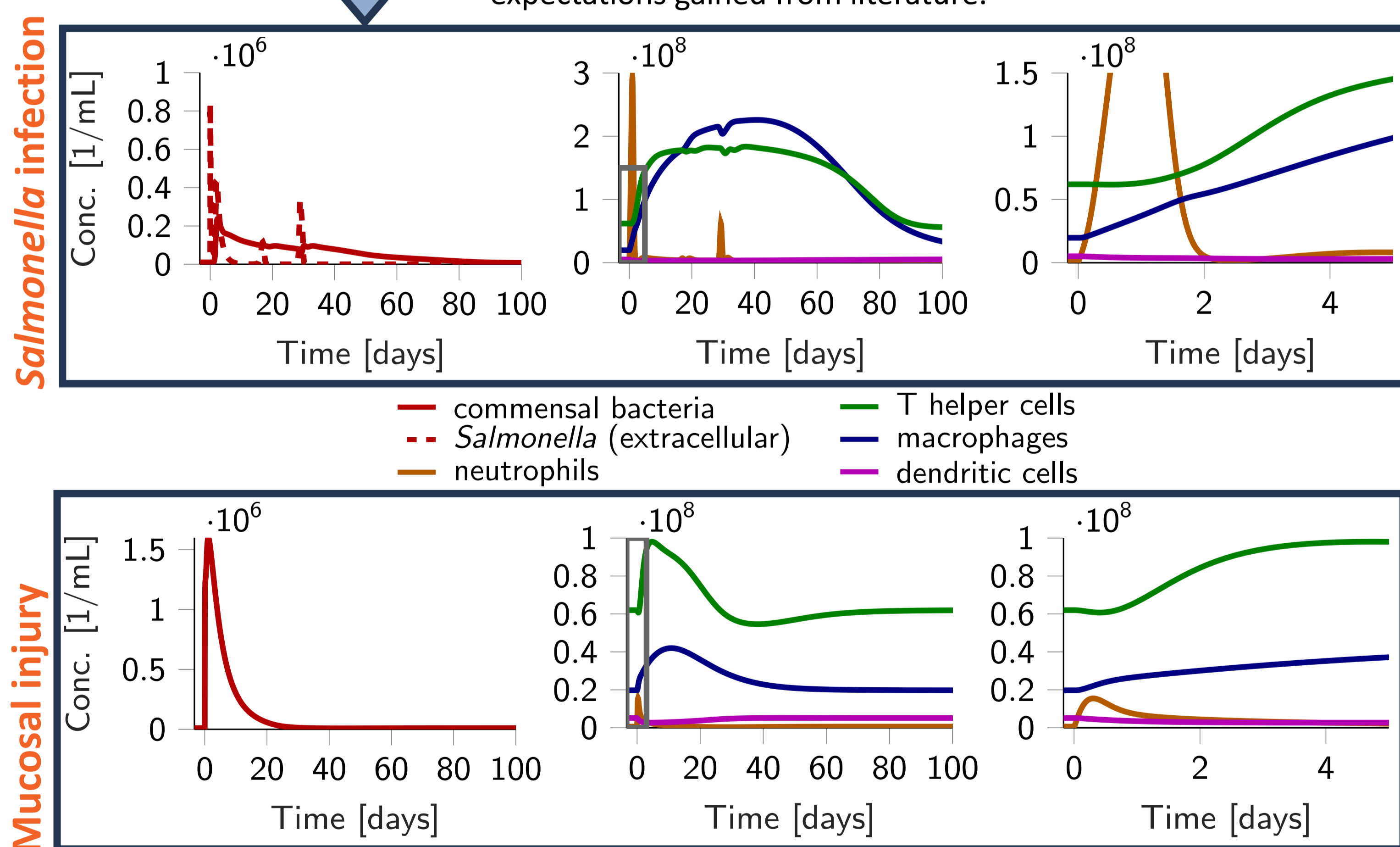
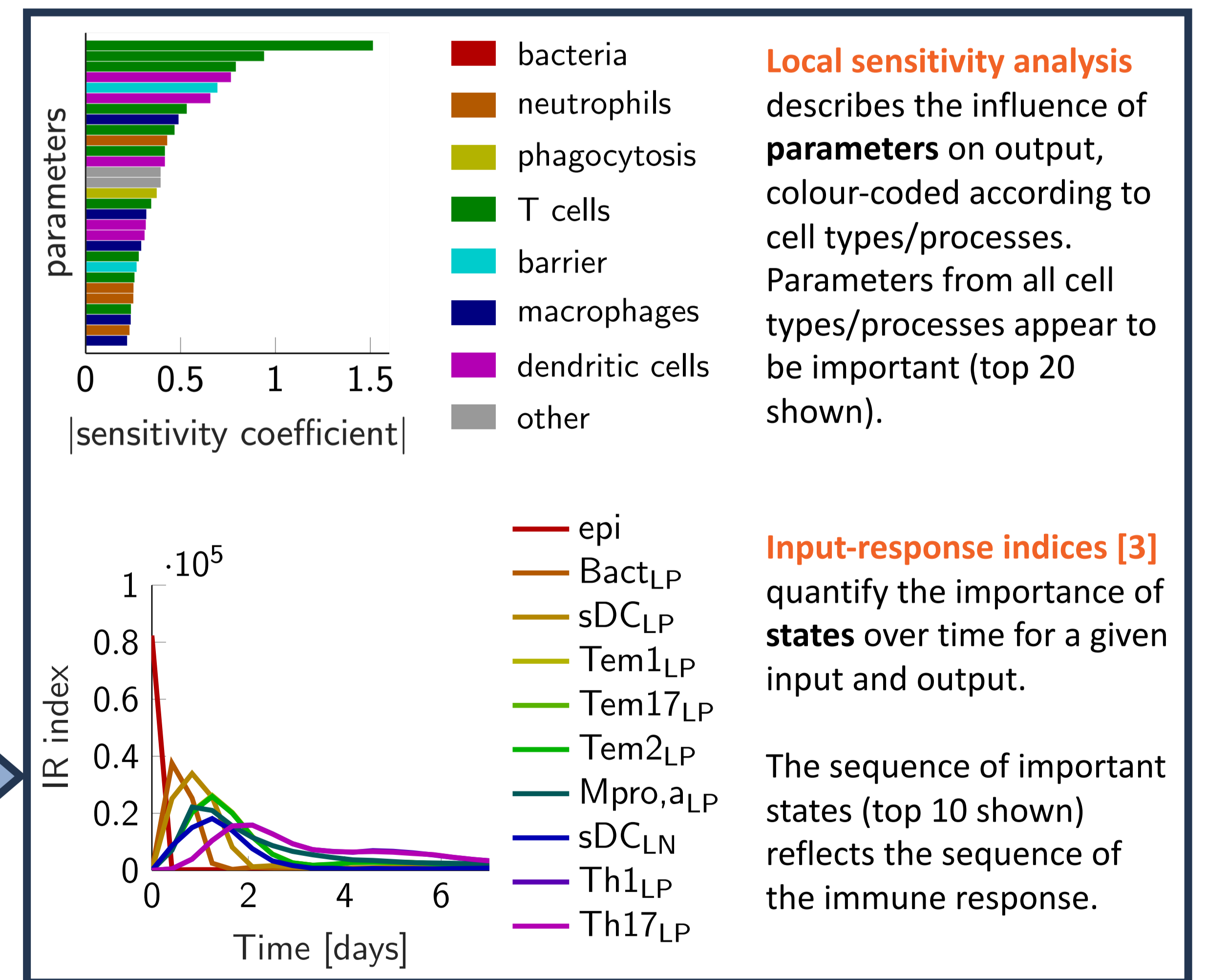


Figure 3 Sensitivity analysis of parameters and states to gain information on important processes for inflammation

As starting point for simulation of chronic inflammation. We use the inflammation scenario of mucosal injury (model input) and the T helper cell concentration as surrogate marker for inflammation (model output).



Outlook

From acute to chronic inflammation

We will search for different **parameter combinations leading to chronic inflammation**, making use of the sensitivity analysis results and available literature about genetic polymorphisms leading to IBD (e.g. [4]). Thereby, a set of **virtual IBD patients** will be generated.

Treatment of IBD

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 of the mAbs).

Variability in treatment outcome

Using simulation of treatment in the set of virtual IBD patients, we aim at analysing possible **underlying mechanisms of high inter-individual variability in treatment outcome** by finding processes with high influence on disease and treatment outcome.

References

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