Towards a systems biology model for inflammatory bowel disease

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Inflammatory bowel disease (IBD)

IBD is characterised by a chronic inflammation in the gastrointestinal tract. There are two major subtypes:

- **Crohn's disease** (CD): located in any part of the gastrointestinal tract, most often ileum and colon; affects all layers of the gut wall
- **Ulcerative Colitis** (UC): restricted to colon; only mucosa [1]

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; e.g. anti-TNF-α therapy leads to remission in a large part of patients, but lacks effect in other patients [2].

Objectives

Our aim is to understand the underlying mechanisms for this behaviour. We propose a systems biology approach, **modelling the cellular processes** in IBD and the effects of various treatments. As starting point we use main ideas from the `model of colonic inflammation' by Wendelsdorf et al. (2010, [3]).

Model description

Dendritic cells

Antigen uptake and activation:

- dendritic cells in lamina propria **take up and present antigen**, then **migrate** to mesenteric lymph nodes
- healthy: dendritic cells **respond poorly** to bacterial stimulation (quiescent); induce regulatory T cells (tolerogenic)
- small fraction of **activated** dendritic cells (responsive to stimulation); induce helper T cells (stimulatory) [4]

T cells

T cell receptor (TCR) activation and proliferation:

- upon contact of dendritic cell and TCR-specific naive/memory T cell: **proliferation** and **differentiation** into effector T cells
  - stimulatory dendritic cells → helper T cells
  - tolerogenic dendritic cells → induced regulatory T cells
- probability of TCR specificity for given antigen: greater for memory T cells than naive T cells
- further stimulation by specific antigen needed for **activation** of effector T cells [4]

Apoptosis

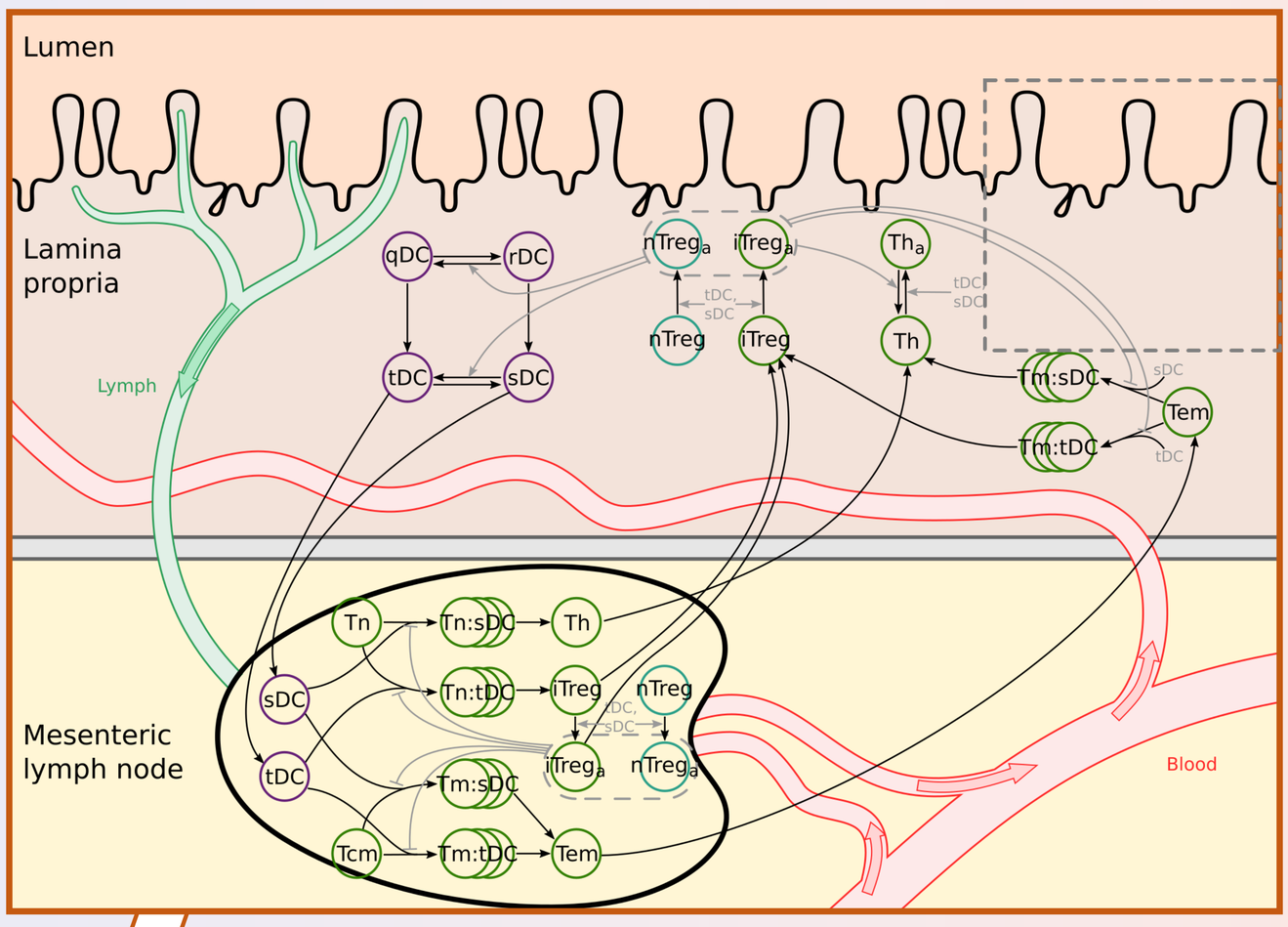
of effector and regulatory T cells:

- activation-induced cell death (AICD): death by TCR re-stimulation, dependent on **interleukin-2** (IL-2) [5]
- activated cell-autonomous death (ACAD): death by cytokine withdrawal (IL-2 withdrawal) [5]
- IL-2 production by proliferating T cells and activated helper T cells [6]
- high IL-2 consumption by proliferating and regulatory T cells; low IL-2 consumption by all other T cells

Regulatory T cells

Effects of induced and regulatory T cells:

- negative influence on activation status of **dendritic cells** [7]
- decrease of **activation probability** of naive/memory T cells by dendritic cells [8]
- inhibition of activated **T helper cells** [7]



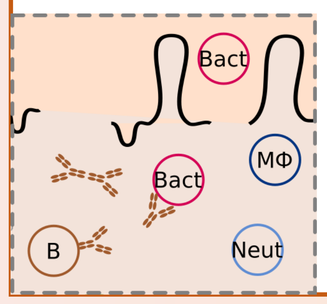
qDC quiescent dendritic cells
rDC responsive dendritic cells
tDC tolerogenic dendritic cells
sDC stimulatory dendritic cells
Tn naive CD4+ T cells
Tm memory T cells
Tcm central memory T cells
Tem effector memory T cells
Th helper T cells
iTreg induced regulatory T cells
nTreg natural regulatory T cells

Figure 1. Schematic of the systems biology model comprising dendritic cells in different activation states and various T cell phenotypes.

IBD

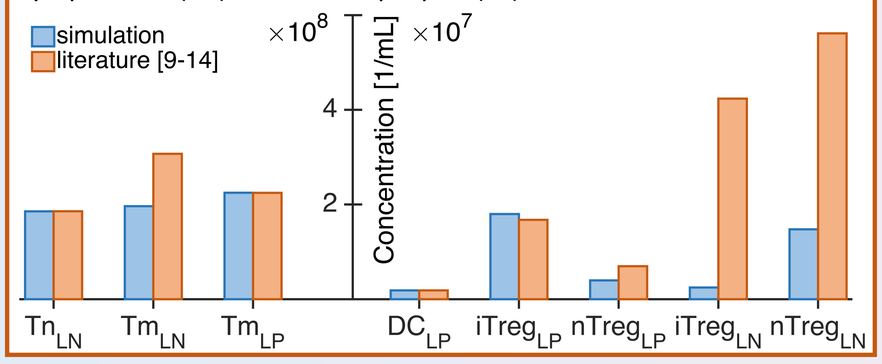
Requirements for simulation:

- chronic inflammation, tissue destruction
- **pathogenesis**: many different genetic and environmental risk factors → accumulation of changes
- definition of **disease status**



Healthy steady state

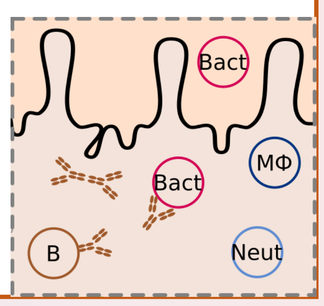
Concentrations of dendritic cells and T cell subtypes in mesenteric lymph node (LN) and lamina propria (LP)



Infection

Requirements for simulation:

- account for **pathogens**
- macrophages, neutrophils (innate immune response), B cells
- positive feedback of **inflammation** on the recruitment rates of various immune cells



IBD therapy

Requirements for simulation:

- account for **pharmacokinetics** (→ concentration in plasma and gut tissue)
- implementation of **drug effects** (e.g. mAbs: account for soluble and membrane-bound TNF-α)
- location of drug effect (blood/tissue)

Further requirements

Future directions

We aim at developing a **combined PK and systems biology** model for quantitative and time-resolved description of cellular processes in IBD and effects of different treatments including mAbs against TNF-α.
This model will then be used to

- account for **inter-individual variability**
- analyse to which extent the model is able to describe both the **responding and non-responding** behaviour to the different treatment options
- potentially explain the published correlations between responsiveness and certain **genetic polymorphisms** (e.g. [15])

With a better knowledge of the inter-individual variability leading to differences in therapeutic outcome, the decisions for **individual therapy** can be optimised.

References

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