A Quantitative Systems Pharmacology Model to Investigate the Crucial Role of Epithelial Damage in the Pathogenesis of Inflammatory Bowel Disease

Julia L. Stolk[1], Douglas W. Chung[2], Piet H. van der Graaf[1,2]
[1] Leiden University, Leiden, The Netherlands; [2] Certara Applied BioSimulation, Sheffield, United Kingdom

"The QSP model explains the recovery of the chronic inflammatory state of the EBF in response to bacterial infiltration and epithelial damage."

Introduction

In inflammatory bowel disease (IBD) patients, there is an imbalance between pro- and anti-inflammatory cytokines [1,2]. When the epithelium gets damaged, **overproduction of pro-inflammatory cytokines** (cyt_{pro}) causes inflammation, damaging the epithelium further, resulting in a severe state caused by chronic inflammation [3].

While loss of **epithelial barrier function** (EBF) is known to play an important role in IBD, current treatment mainly targets the resulting chronic inflammation [4].

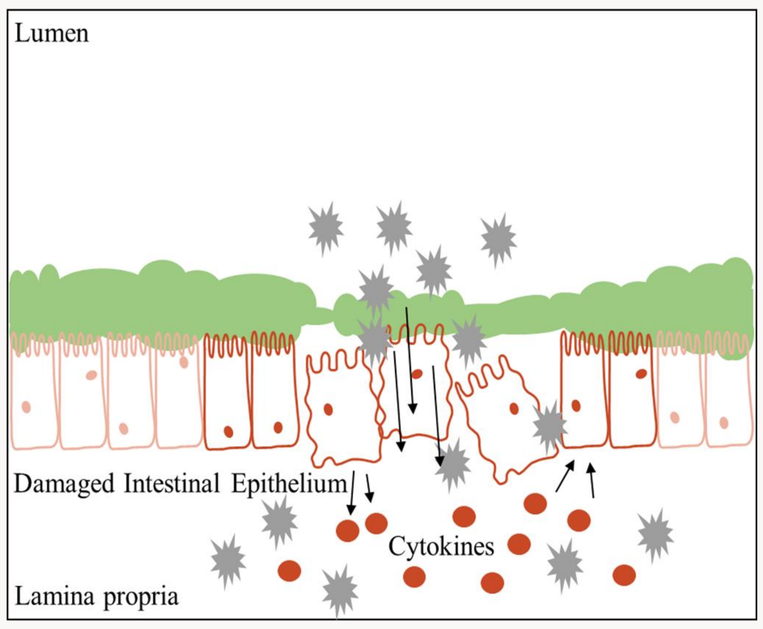

Figure 1 In IBD, cyt_{pros} are secreted in response to epithelial damage resulting in a further compromised EBF [2,5].

Aim

Build a **QSP model** investigating the crucial role of a **damaged EBF** in **IBD pathogenesis**.

Methods

- Equations were implemented to **describe** the **dynamics** and **interactions** of epithelial cells, cyt_{pro}, pathogenic bacteria, mucus function and EBF.
- *In vitro* and *in vivo* experimental data were interpreted by formalizing **data models** to relate cyt_{pro} levels, transepithelial electrical resistance (TEER), and dextran permeability to the QSP model outputs.
- The model was further tested by a **local sensitivity analysis**.

The EBF Model

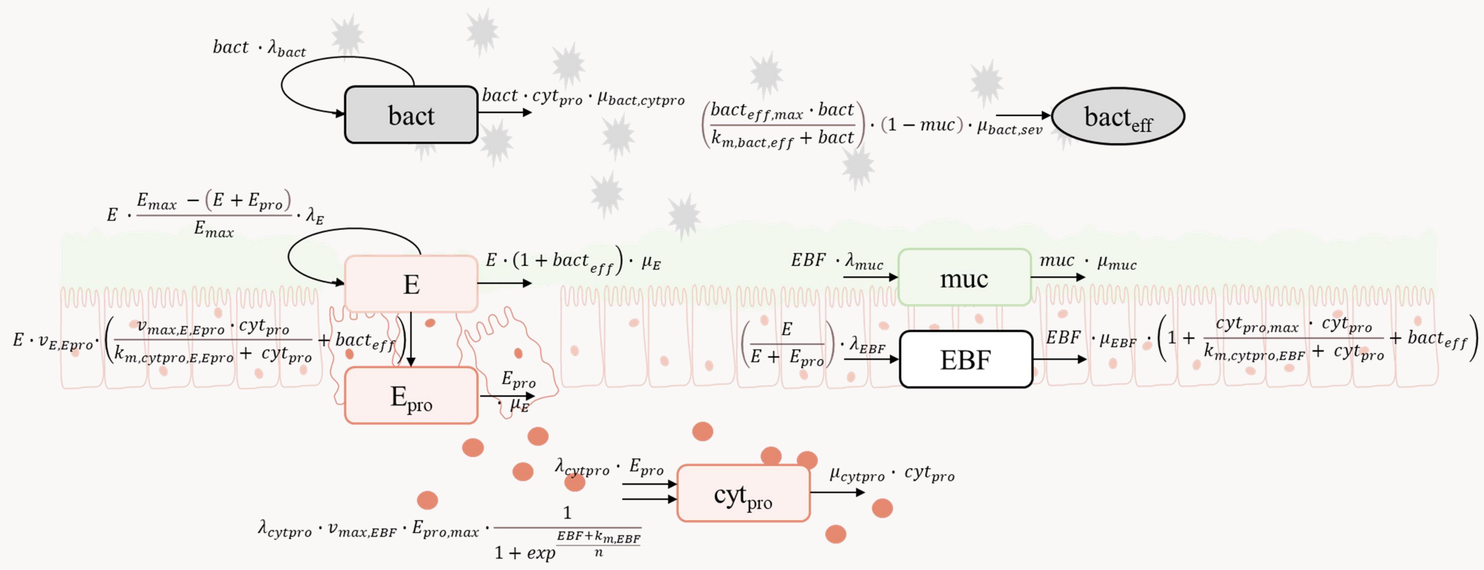

Figure 2 The EBF model consists of six ordinary differentiation equations (ODEs), describing the dynamics of healthy epithelial cells (E), pro-inflammatory epithelial cells (E_{pro}), cyt_{pro}, pathogenic bacteria (bact) and their effect ($bact_{eff}$) , mucus function (muc) and EBF, and how they interact and react to epithelial damage and infiltrations of pathogens. Squares represent variables described by ODEs and circles represent variables described by analytical equations.

Results

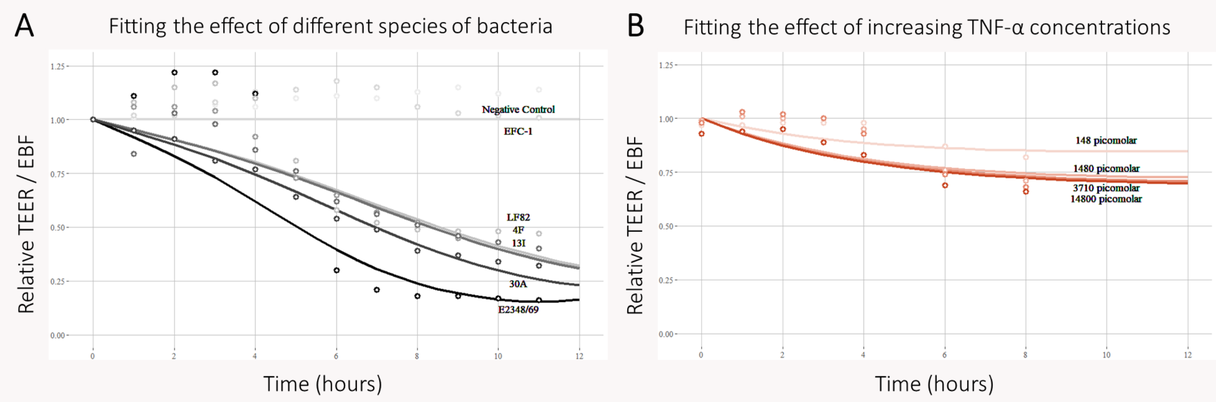

Figure 3 The model can fit the *in vitro* effect of different bacteria species (**A**) [6] and increasing concentrations of TNF-α (**B**) [7] on the TEER in Caco-2 cell monolayers, which directly translates to EBF.

Figure 4 The model can fit data of experiments where moderate and severe colitis was induced by administering C57BL/6 mice with dextran sodium sulphate for five or seven days, respectively. Data models were assembled to quantify EBF and cyt_{pro} measurements.

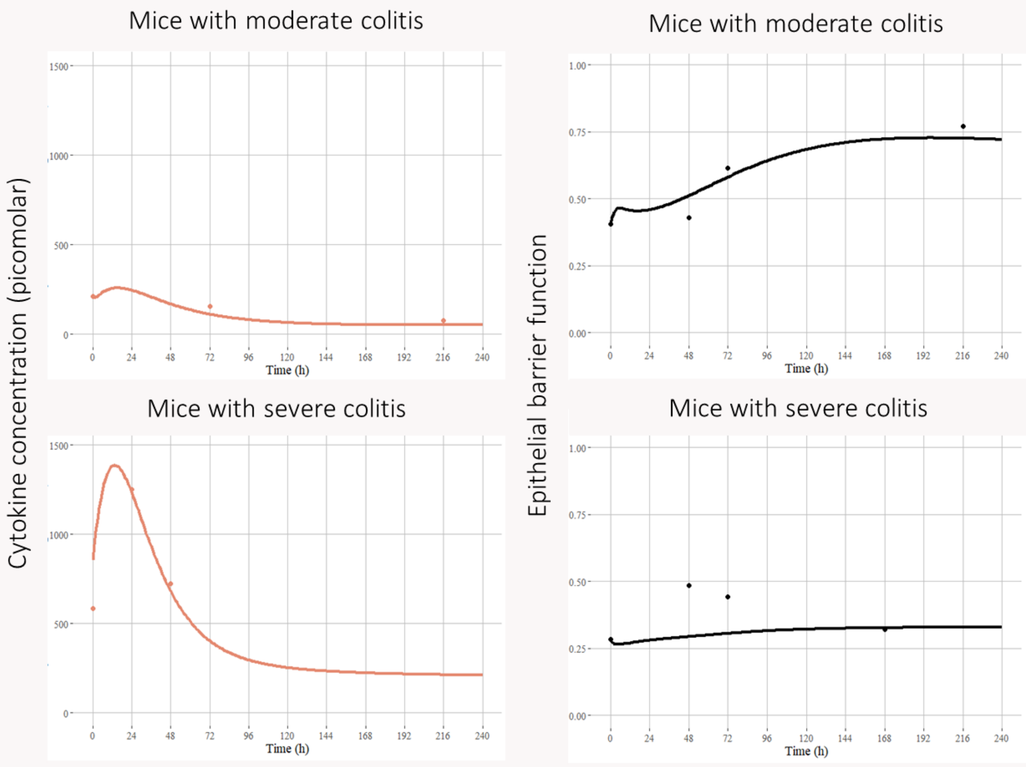

Table 1 Key model parameters. λ: growth rate, μ: death rate.

Parameter	*In vitro* value	*In vivo* moderate value	*In vivo* severe value
λ_{bact} in h^{-1}	0	$8 \cdot 10^{-3}$	$8 \cdot 10^{-3}$
$\mu_{bact,cytpro}$ in L/h	$1.85 \cdot 10^{-3}$	$1.33 \cdot 10^{-4}$	$4 \cdot 10^{-5}$
λ_E in h^{-1}	$6.30 \cdot 10^{-3}$	33.6	33.6
μ_E in h^{-1}	$1.25 \cdot 10^{2}$	0.67	0.67
λ_{cytpro} in h^{-1}	$9.39 \cdot 10^{-6}$	$3.69 \cdot 10^{-5}$	$3.69 \cdot 10^{-5}$
μ_{cytpro} in h^{-1}	$8.49 \cdot 10^{-2}$	$6.46 \cdot 10^{-2}$	$6.46 \cdot 10^{-2}$
λ_{muc} in h^{-1}	0.17	0.19	0.19
μ_{muc} in h^{-1}	0.18	0.20	0.20

- The EBF model can **simulate** a healthy epithelium and epithelial damage after bacterial infiltration or inflammation.
- **First** model to **explain** experimental *in vitro* data, and *in vivo* mice biology.

Conclusion

- The EBF model **explains** the EBF in response to bacterial infiltration and epithelial damage for a **healthy gut** – where the barrier can recover, and for an **IBD scenario** – where chronic inflammation occurs.
- **Further integration** into existing mechanistic models of gut inflammation in IBD to enable the investigation of new classes of therapeutics targeting **epithelial-microbe interactions**.

References

1 Friedrich, M. *et al.*, Mucosal Immunol (2019)
2 Neurath, M. F. *et al.*, Nat Rev Immunol (2014)
3 McGuckin, M. A. *et al.,* Inflammatory Bowel Diseases (2009)
4 Thoo, L. *et al.,* Springer Nature (2019)
5 Coskun M. *et al.*, Front Med (2014)
6 Sasaki, M. *et al.,* Laboratory Investigation (2007)
7 Wang, F. *et al., Gastroenterology* (2006)

Acknowledgements

PAGE attendance of JLS was made possible through financial support by the PAGE conference.

julia.stolk@outlook.com