

Validation of a Network Systems Pharmacology model for Inflammatory Bowel Disease



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BACKGROUND AND OBJECTIVES

Inflammatory Bowel Disease (IBD) is a gastrointestinal tract disorder characterized by periods of remission and relapse causing functional impairment of the gut wall. IBD includes Crohn Disease (CD) and Ulcerative Colitis (UC) [1]. The objective of the current work was to validate a robust Systems Pharmacology (SP) model for Inflammatory Bowel Disease (IBD) able to characterize the main IBD components and its dynamics.

METHODS

NETWORK BUILDING

The development of the theoretical disease network was based on an exhaustive bibliographic review. The network contains 43 nodes and 298 interactions (*Fig 1*).

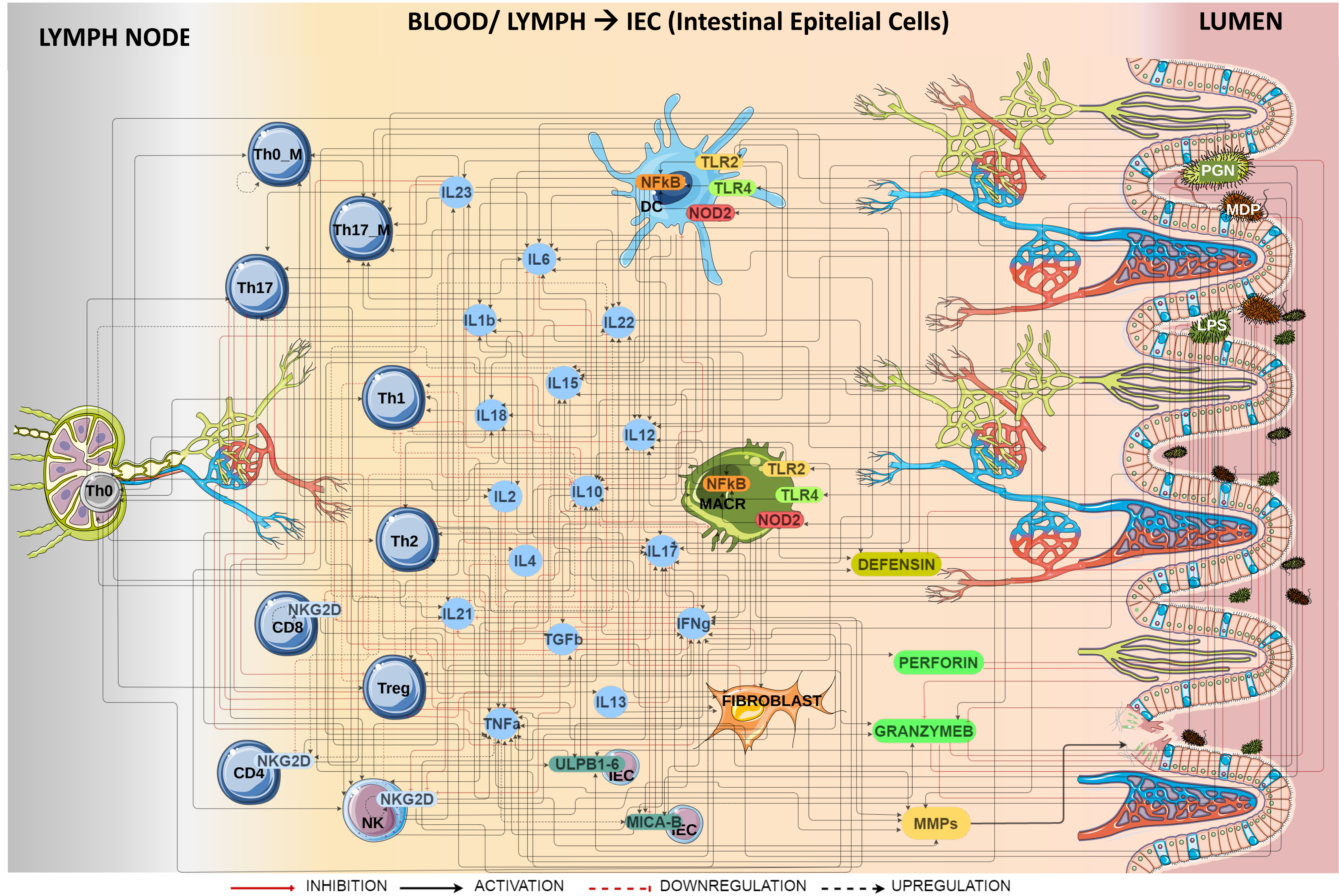


Figure 1. Graphical representation of the Boolean Network for IBD. Input nodes are the microbial antigens Lipopolysaccharide (LPS), Muramyl dipeptide (MDP) and Peptidoglycan (PGN). The output node is MMPs, responsible of tissue damage.

Once the most relevant relationships were identified, the network was built using Boolean functions[2]. This Boolean Network model was implemented in the SP platform SPIDDOR[3].

NETWORK ROBUSTNESS

Robustness in Boolean networks generally depends on **network connectivity**. We performed a **perturbation analysis** in our IBD model to study its robustness[4] by simulating the effect of **single blockage of each node** (column) on **each of the other network nodes** (row). The result is explained in a heatmap with a hierarchical cluster of the nodes that cause similar alterations.

RESULTS

NETWORK ROBUSTNESS

The network perturbation analysis indicates that our SP model for IBD is robust.

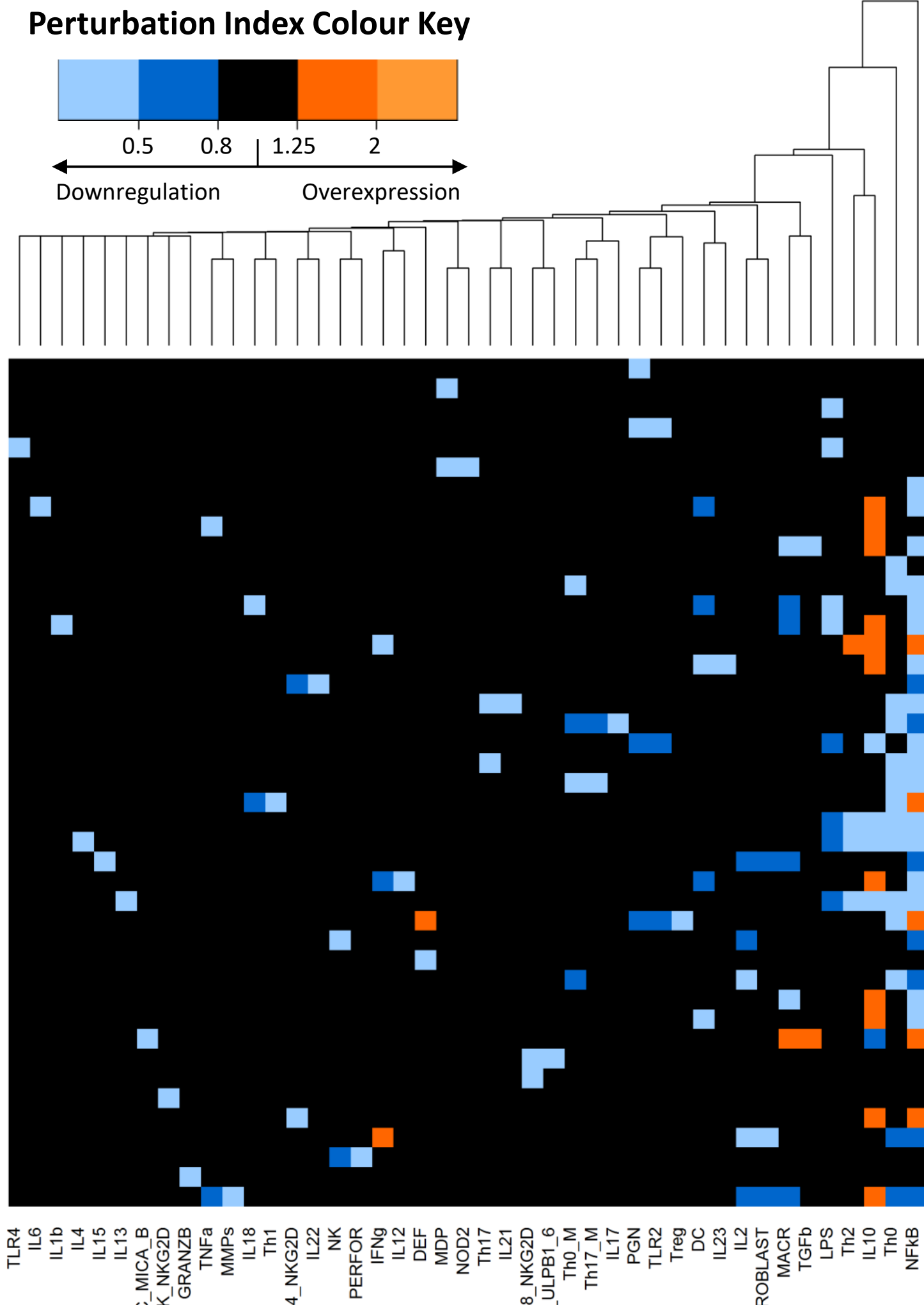


Figure 2. IBD network perturbation analysis and clustering.

CONCLUSIONS

The proposed SP model represents a robust modelling tool for target and therapy identification, as well as an in silico platform to test a variety of therapy combinations. The model can be used to better understand and interpret, from a most molecular point of view, clinical trials results.

MODEL VALIDATION

The network was validated following **two different approaches** based on network based simulations, where it was assumed **chronic exposure** to three different types of microbial antigens (PGN, MDP and LPS):

- (I) Comparison of simulation results after reaching the attractor state for **every node** of the network with the **alterations reported in the literature** for IBD patients as listed in *Table1*.
- (II) Comparison between simulations and results reported in **clinical trials** for five investigated therapies: **anti-IFN γ** , **anti-TNF α** , **anti-IL17**, **human recombinant IL10** and **Granulocyte and Monocyte Apheresis(GMA)**. Reported CDAI (Crohn Disease Activity Index) was compared with the attractor level of the MMPP node.

Table 1. Expression of our network nodes in IBD patients. Information extracted from the literature.

NODE	EXPRESSION	NODE	EXPRESSION	NODE	EXPRESSION	NODE	EXPRESSION
PGN	Altered	IL1b	Upregulated	Th2	Upregulated	DC	Downregulated in Blood- Upregulated in mucosa
MDP	Altered	IFN γ	Upregulated	IL4	Altered	IEC_MICA_B	Upregulated
LPS	Altered	IL23	Upregulated	IL15	Upregulated	IEC_ULPB1_6	Upregulated
TLR2	Upregulated	IL22	Upregulated	IL12	Upregulated	CD8_NKG2D	Upregulated
TLR4	Upregulated	IL21	Upregulated	IL13	Upregulated	NK_NKG2D	Unknown
NOD2	Altered	IL17	Upregulated	Treg	Downregulated in Blood- Upregulated in mucosa	CD4_NKG2D	Upregulated
NFkB	Altered	IL10	Upregulated	NK	Upregulated	FIBROBLAST	Upregulated
IL6	Upregulated	Th1	Upregulated	DEF	Upregulated	MMPs	Upregulated
TNFa	Upregulated	Th17_M	Upregulated	IL2	Upregulated	PERFOR	Altered
TGFb	Upregulated	Th1	Altered	MACR	Upregulated	GRANZB	Upregulated

MODEL VALIDATION

(I) SIMULATIONS

SP model has satisfactorily been validated with data from the literature (*Table1*).



Figure 3. Relative expression of nodes after the simulation of healthy subjects and IBD patients.

(II) CLINICAL TRIALS

- The outcome of the current **approved anti-TNF α** therapy and the **promising therapy GMA** was replicated with a substantial **decrease in MMPs** (close to 30%).
- For the **failed treatments (anti-IL17, rhIL-10 and anti-IFN γ)** only a slight decrease (6% for anti-IL17 and 3% for rhIL-10) and an increase (15% for anti-IFN γ) of MMPs simulated expression was obtained, which is in line with CDAI score in clinical trials.

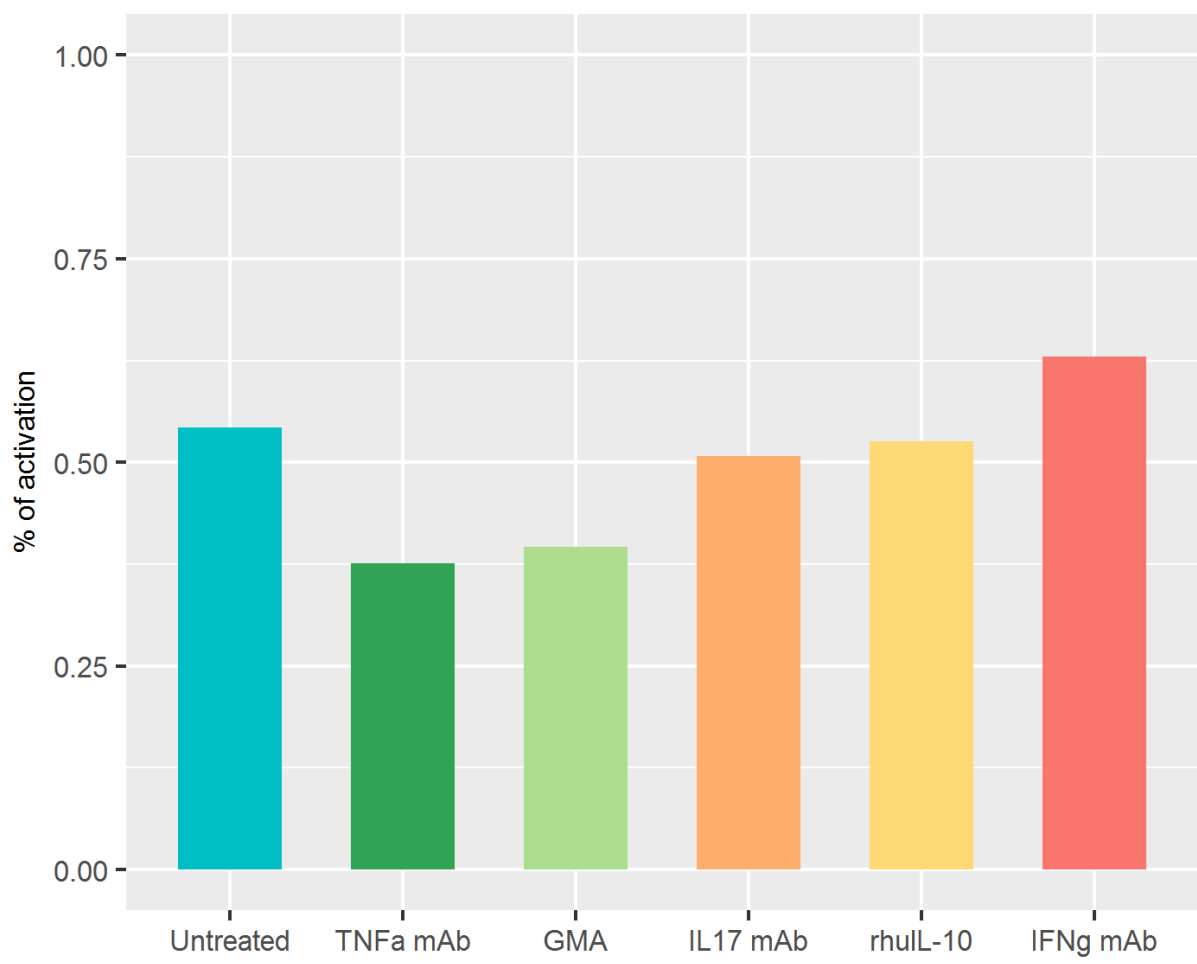


Figure 4. MMPs relative expression for IBD simulated subjects under different therapies.

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