

Quantitative Systems Pharmacology model for the key Interleukins involved in Crohn's Disease

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BACKGROUND AND OBJECTIVES

Crohn's Disease (CD):

Is a **complex inflammatory bowel disease** that causes a **functional impairment of the gut wall**. Its pathogenesis appears to involve several defects in different immune mechanisms (1).

Background:

- The reported **lack of effectiveness** in the **standard of care** together with the worldwide **increase in CD incidence** (2) require the **application of techniques** aiming to find new targets and therapeutic strategies.
- The available knowledge (3,4) can be integrated into a **single QSP model**.

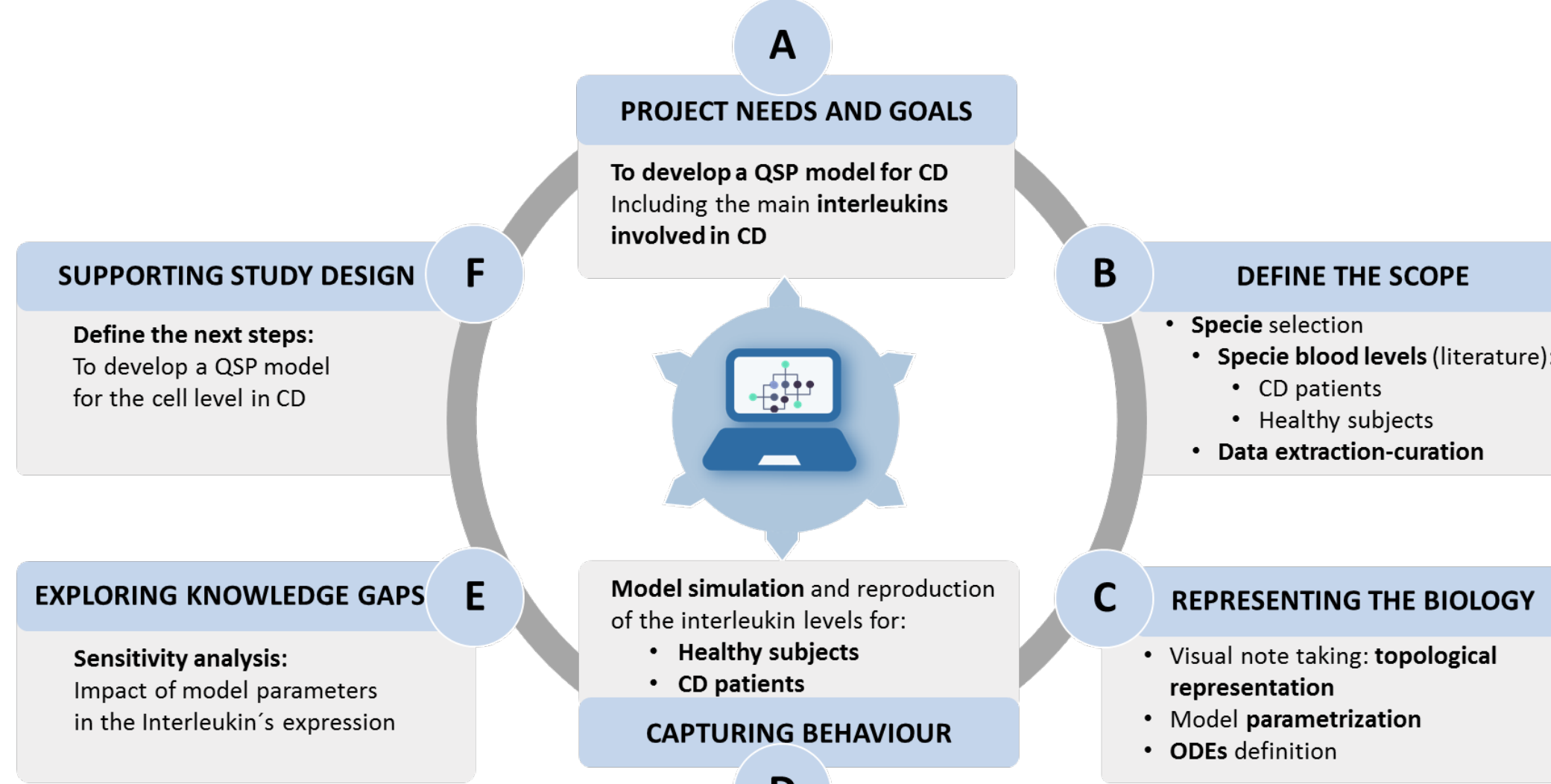


Figure 1: Adaptation of the six-stage workflow for robust application of SP modelling proposed by Gadkar et al. (5) to the CD scenario

Objective:

To develop a **QSP model** in **humans** characterizing the dynamics of the main **interleukins (ILs)** involved in **CD** using previous modelling efforts as starting point (3-4), and incorporating new relevant molecular pathways in CD.

In this work we have adapted the six-stage workflow (Fig. 1) for robust application of SP modelling (5) to the CD scenario.

METHODS

1. SCOPE DEFINITION

Steady state (SS) levels of each of the **ILs** and **cells** were obtained for **healthy subjects** and **CD patients** based on a **literature** search and the average blood concentration ($\bar{x}_{wtd}$) was calculated as:

$$\bar{x}_{wtd} = \frac{\sum_{i=1}^n (\bar{x}_i \times w_i)}{\sum_{i=1}^n w_i}$$

$\bar{x}_i$: average plasma concentration of the specie of interest

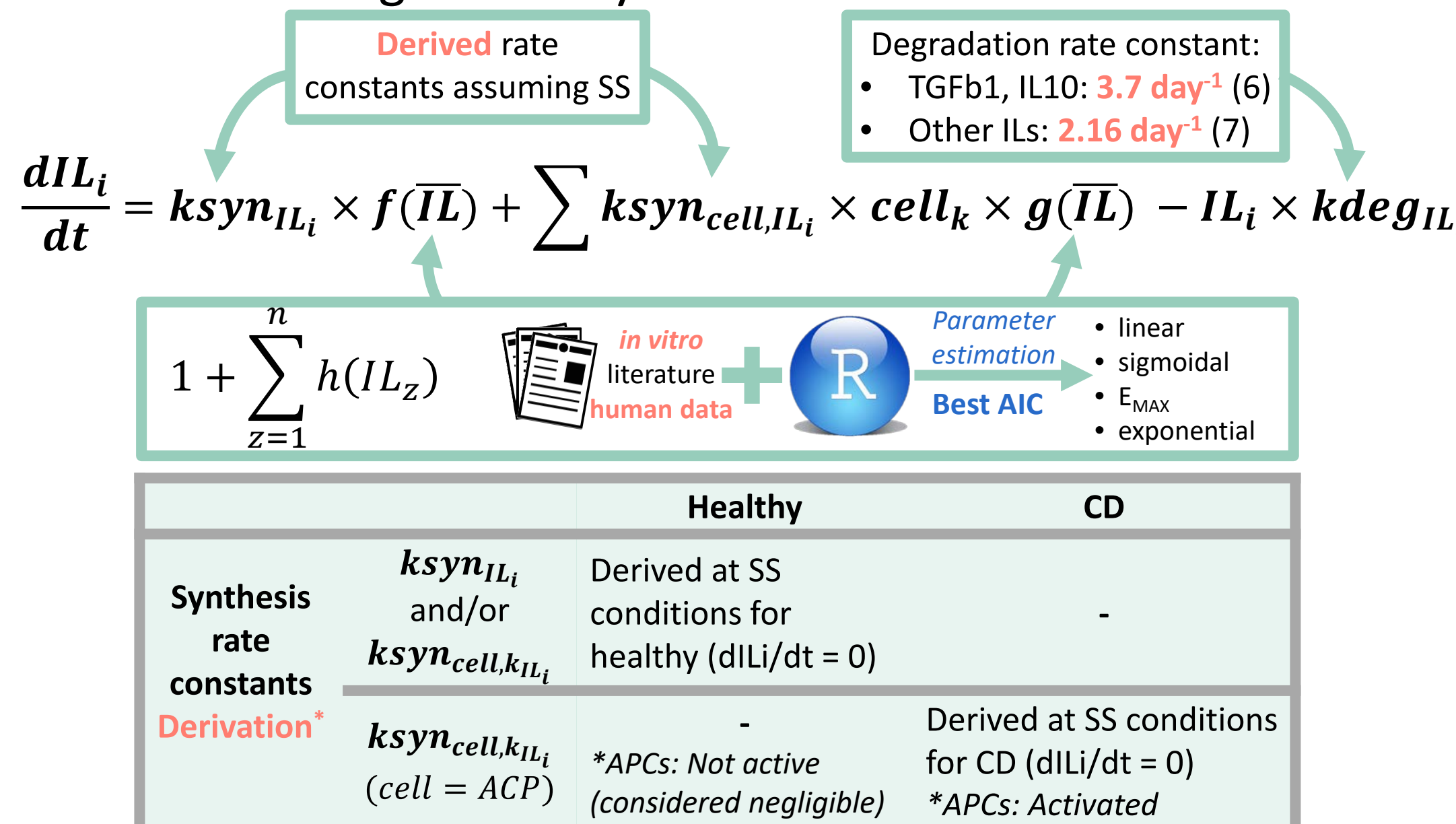
w_i : number of individuals reported in the i^{th} study

2. GRAPHICAL REPRESENTATION

Visual note-taking diagrams were generated for each of the interleukins sub-models.

3. MODEL PARAMETRIZATION AND ODE DEFINITION

Parameters and ordinary differential equations (ODEs) characterizing model dynamics were obtained as follows:



*Fixed: (i) Initial conditions, (ii) Kdeg values (iii) $h(IL_i)$ estimates

4. CAPTURING BEHAVIOUR

The model was implemented in **SimBiology®** (MATLAB® R2018b).

Model curation:

Model evaluation: run 1000 simulations, where the ILs and cells **initial conditions** were randomly fixed from uniform distributions (between the literature reported ranges in CD).

Therapy simulation:

Simulation of the maximum concentration achieved in a clinical study in CD patients (**1 or 6 ng/mL**), mimicking the exposure to two doses of recombinant human IL10 (**rhIL10**) (8), administered as an **intravenous bolus** during **seven consecutive days**.

RESULTS

1. SCOPE DEFINITION

A total of **21 species** representative of the innate and adaptive immune system in CD were **included in the model**:

Table 1. Circulating levels for healthy subjects and CD patients.

Specie	Healthy subjects mean ±SD (range)	CD mean ±SD (range)
MACRact	0	1.00 *10 ⁴
DCact	0	1.32 ± 3.71 * 10 ⁴
Th0act	0	1.95 *10 ⁵
Th2	1.11 ± 0.69 *10 ⁴	1.45 ± 0.90 *10 ⁴
Th1	5.39 ± 1.04 *10 ⁴	1.23 ± 0.46 *10 ⁵
Th17	1.28 ± 0.77 *10 ⁴	1.93 ± 0.89 *10 ⁴
Treg	2.83 ± 0.70 *10 ⁴	2.88 (0.07-4.84) *10 ⁴
IFNγ	20.95 (1.00-275.00)	30.74 (0-105.00)
TNFα	8.01 (0.61-42.00)	11.00 (0-976.00)
IL4	2.39 (0.01-15.62)	3.00 ± 1.30
IL10	6.12 (0.14-156.60)	26.53 ± 59.23
TGFβ1	2.72 ± 1.46 *10 ⁴	4.93 ± 3.74 *10 ⁴
IL12	13.65 (1.00-56.30)	33.04 ± 31.66
IL1b	1.02 ± 0.81	9.70 ± 11.00
IL18	2.42 ± 0.90 *10 ⁴	5.46 ± 0.32 *10 ⁴
IL2	2.47 (0.25-15.90)	7.53 (0-22.50)
IL17	20.16 (0-180.00)	44.50 ± 70.76
IL23	94.91 (7.80-439.00)	192.92 ± 213.52
IL6	5.99 (0-32.00)	38.46 (0-150.00)
IL22	24.55 (2.00-60.80)	37.44 ± 6.58
IL15	3.44 (0-16.77)	9.00 ± 15.35

Cells units: cells/mL. IL units: pg/mL

3. PARAMETRIZATION AND ODES

The QSP model includes **14 ODEs**, one for each IL, and **98 parameters** accounting for the different inter-relationships. **IL12 is shown as an example**:

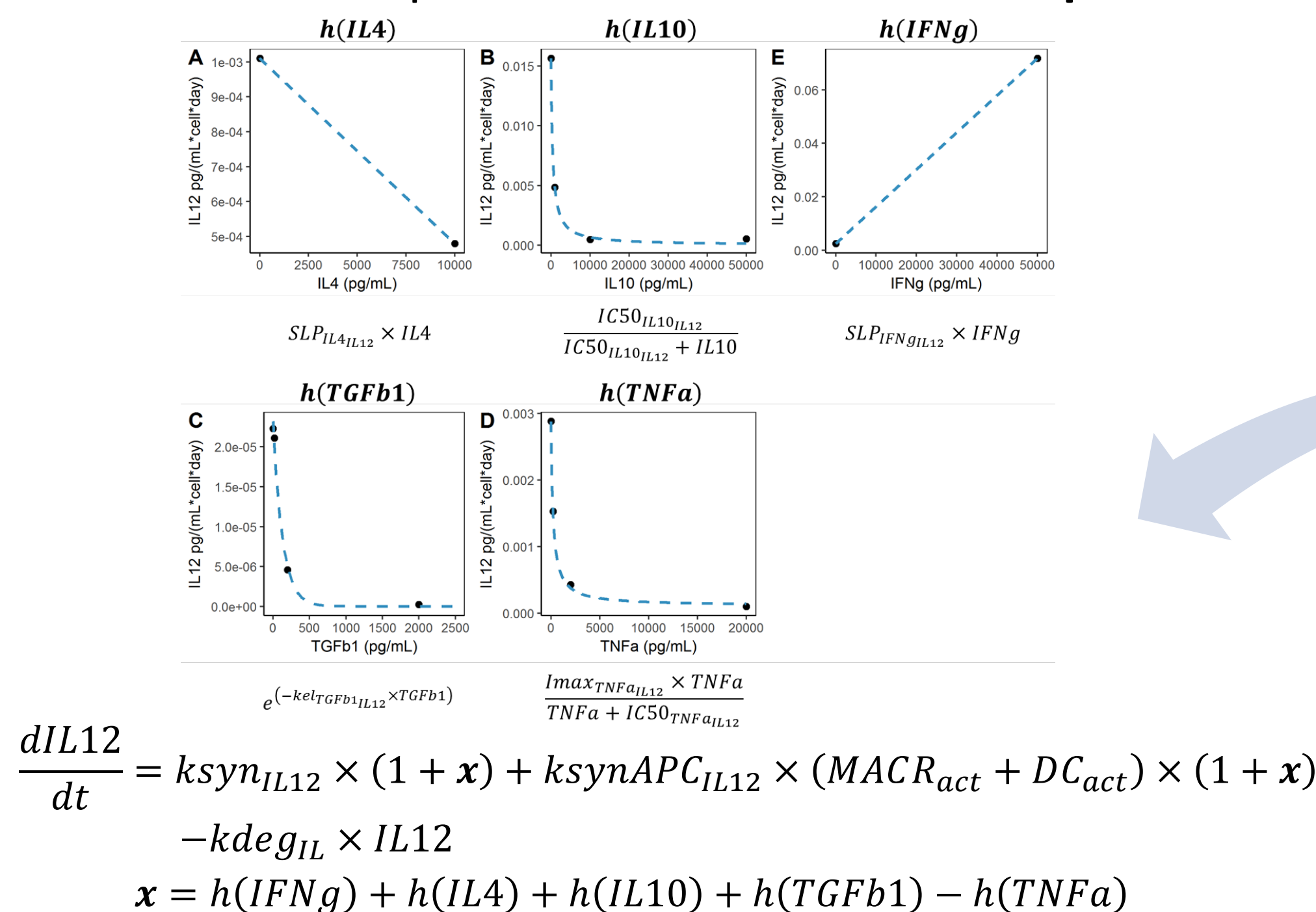


Figure 3: Graphical representation and mathematical expression of the different models characterizing the ILs influence on IL12 synthesis. The dashed blue lines refer to the simulated model and black points to the in vitro data obtained from the literature: A (9), B (10), C (11), D, (12) and E (10).

CONCLUSIONS

A **QSP model** describing the dynamics of 14 ILs in human blood oriented to **CD** has been **developed, implemented** and its **robustness evaluated**. This work contributes with **detailed models for each IL** and corresponding parameter values that might be **re-used in other therapeutic areas** in which ILs play a relevant role, providing a **repository summarizing up to date** the most **relevant literature in CD**, and full **implemented model in Simbiology**. As any QSP model, the current framework is a living project in which the dynamics of the cells are being considered, expanding the applicability of the network to **evaluate therapeutics** acting on those specific pathways.

2. GRAPHICAL REPRESENTATION

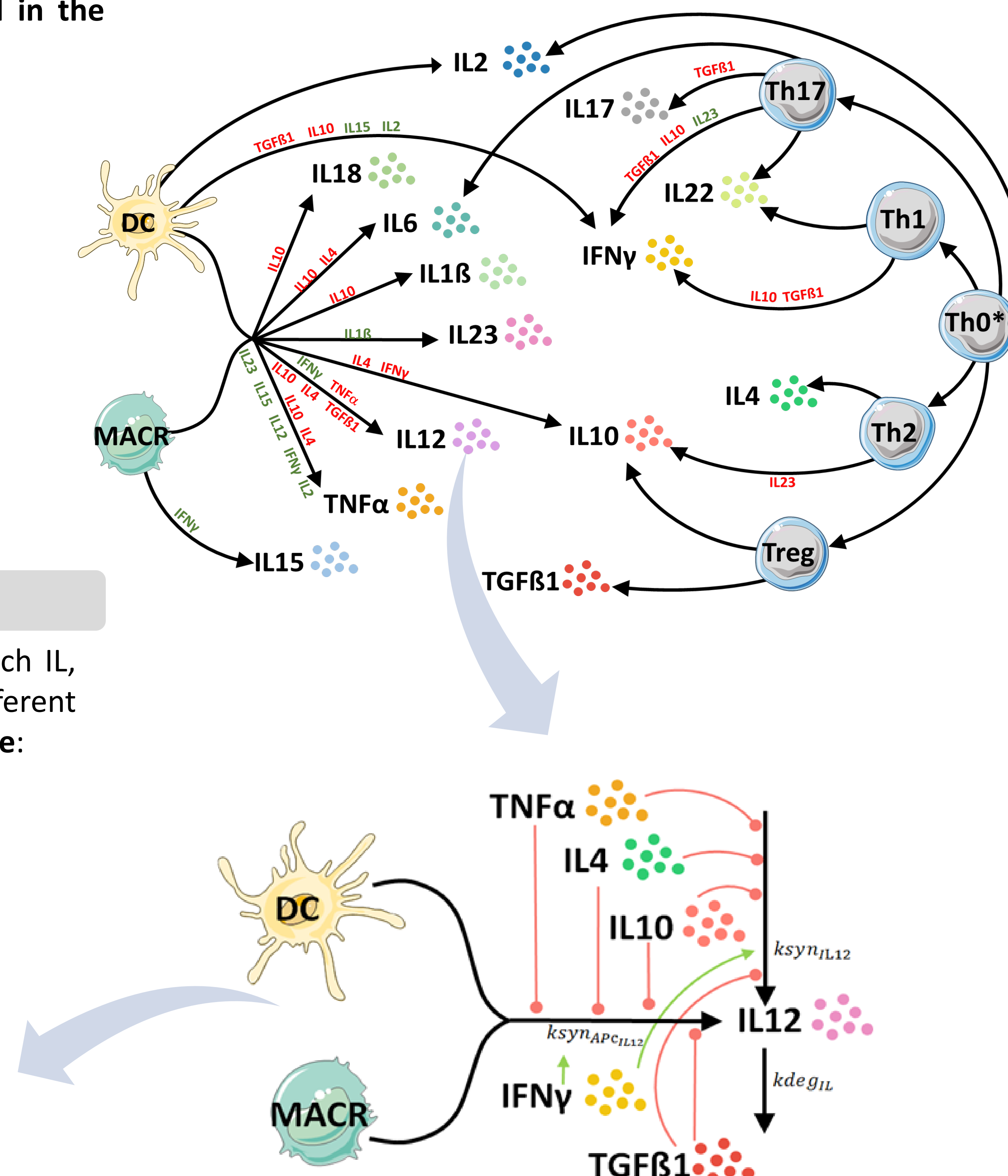


Figure 2: Upper part: Graphical representation of the CD model. The ILs in charge of synthesis stimulation are depicted in green colour, while the ones inhibiting those syntheses are represented in red. Bottom part: Example of the graphical representation of IL12. Synthesis stimulation is represented by green arrows and inhibitions are represented by red lines with a round edge. Figure created using Servier Medical Art (smart.servier.com).

4. CAPTURING BEHAVIOUR

Model curation:

Random values within the physiological range of the model components did not produce non-physiological SS levels for any of the ILs in CD or healthy (*not shown*).

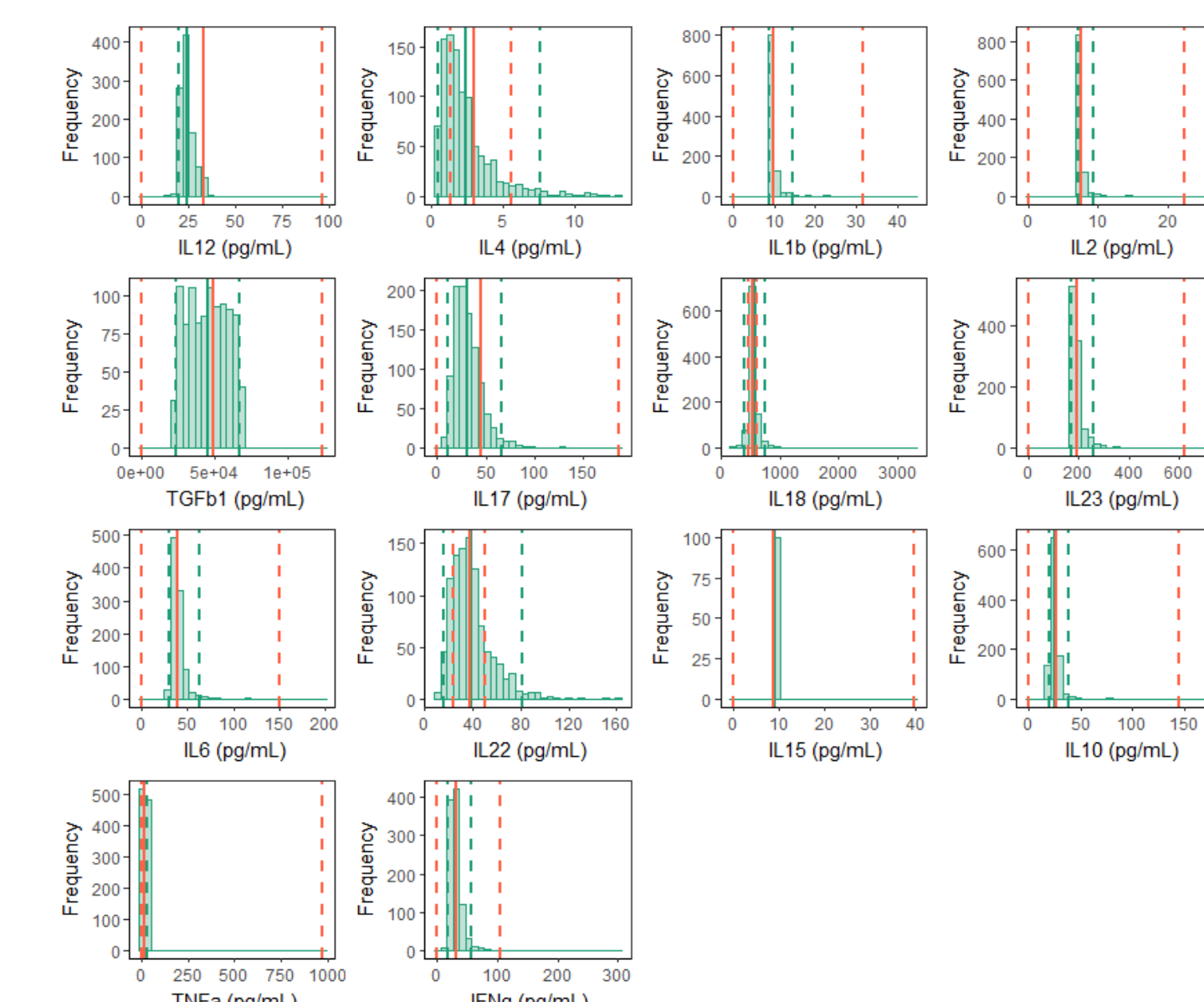


Figure 4. Light green and red colours represent the simulated vs reported concentrations in the literature (Tab.1) respectively. Solid lines account for the mean while dashed lines represent the reported ranges (Tab. 1) or 2.5-97.5th percentile for the simulations.

Therapy simulation:

At the **lower dose**, **IFNγ**, **IL18** and **TNFα** levels were reduced towards the **healthy state**, in agreement with the general outcome of the study (8).

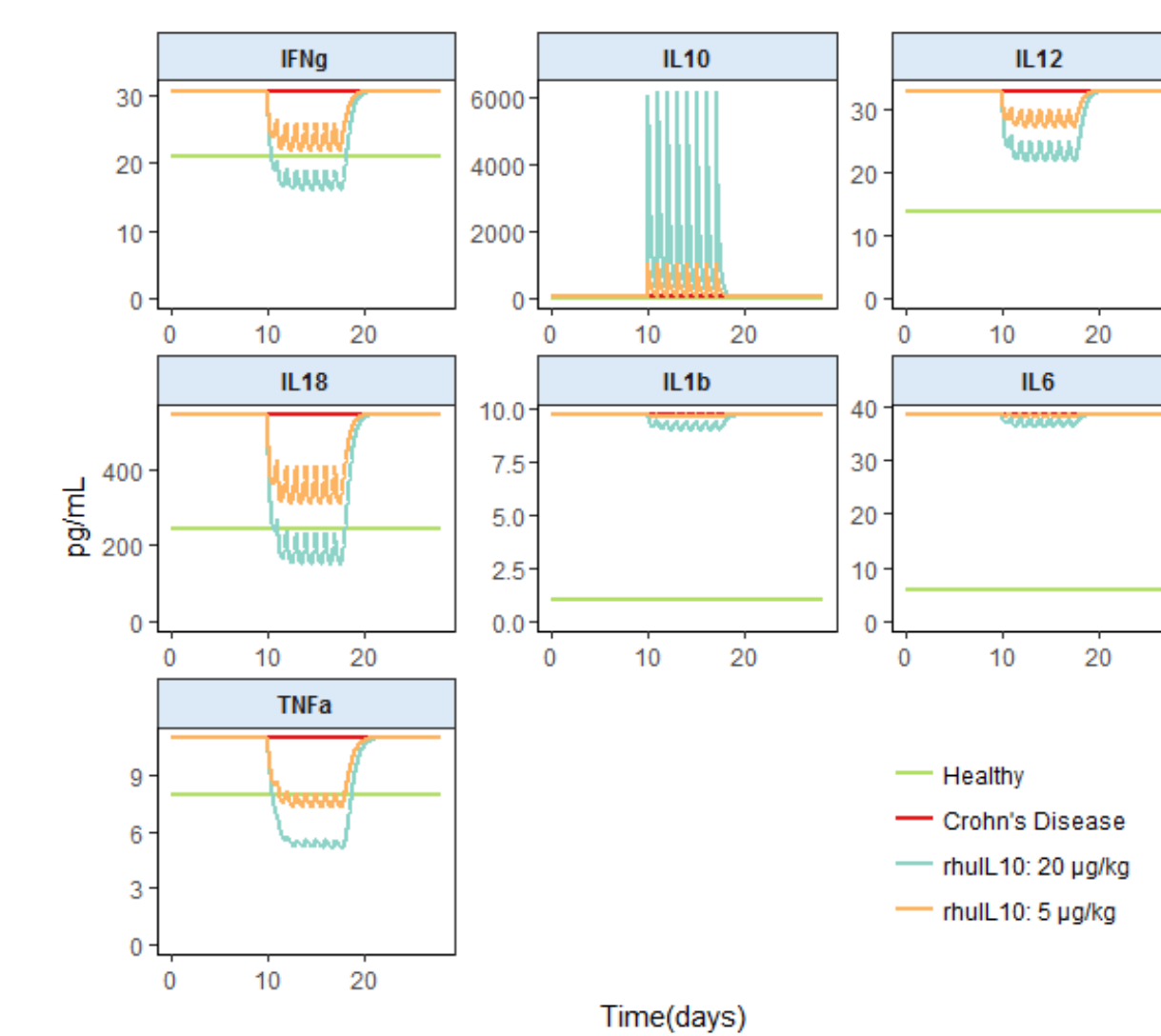
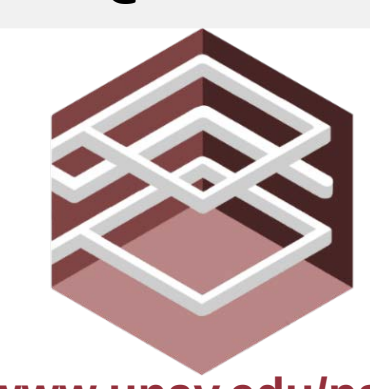


Figure 5. Simulated profiles of the affected rhIL10 ILs in healthy state, non-treated and treated CD with two doses of rhIL10 as described previously. The red and green lines represent the CD and healthy values from the literature (Tab. 1).

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