QSP Model of Rheumatoid Arthritis
Capturing range of clinical responses to Methotrexate and anti-TNFα therapies

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1. Introduction

Quantitative Systems Pharmacology (QSP) models connect knowledge from biological interactions to observed behaviour in clinical trials, Fig 1.1[1]. Mechanistic Physiological modelling is useful in answering several scientific questions related to development of novel therapies.

Rheumatoid Arthritis (RA) is a chronic Auto-Immune disease, affecting the synovial tissue as shown in Fig 1.2[2]. The disease restricts motion in affected joints, causes pain, can severely affect quality of life. Biologic and Synthetic DMARDS are used for treatment of RA.

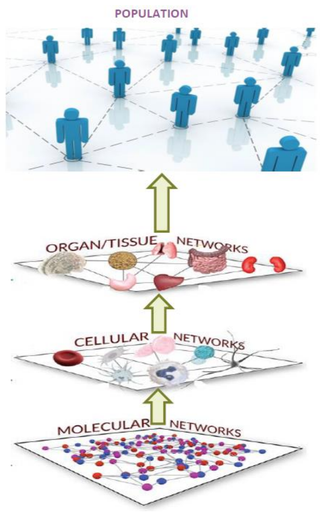

Fig 1.1[1] : A QSP model integrates knowledge from multiple scales

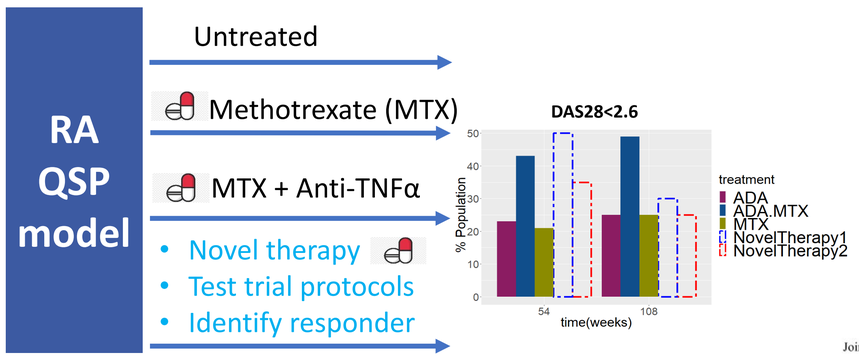

Fig 1.3 : Sample use cases for Vantage RA QSP model

The Vantage Rheumatoid Arthritis model (Vantage RA QSP model) incorporates the latest understanding of RA pathophysiology. The model is developed with MATLAB Simbiology. It captures the relevant physiological mechanisms in moderate to severe RA patients. The model has been calibrated to Methotrexate and Anti-TNFα therapies, with DAS28-CRP as the primary clinical readout at this time.

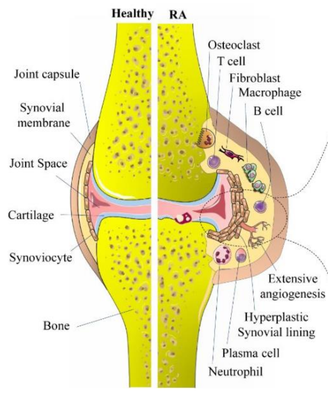

Fig 1.2[2] : An average joint represented in the model

Model scope, assumptions and limitations

- The model represents a single 'average' inflamed joint of a moderate-severe RA
- Subjective clinical score DAS28 in RA is calculated as a function of inflammatory cell densities and cytokine concentrations
- The model captures the disease in steady state; it does not address disease progression
- Flares are not being modelled

2. Model species and interaction network diagram

The mechanisms leading to Rheumatoid Arthritis are not fully understood, but in patients, the synovium is observed to host excessive densities of immune cells. This results in an imbalance of pro and anti-Inflammatory immune response. The main players observed in the synovium are shown below:

- **Immune cells**: Macrophages,B cells, Th1, CD8, T reg
- **Structural cells**: FLS, Osteoclasts, Osteoblasts, Chondrocytes
- **Pro-inflammatory cytokines**: TNFα, IL1β, IL6, IL17, IFNϒ, GMCSF
- **Anti-inflammatory cytokines**: IL10, TGFβ
- **Other species**: Endothelial cells, MMP, VEGF, Auto-antibodies

Model Effect Diagram

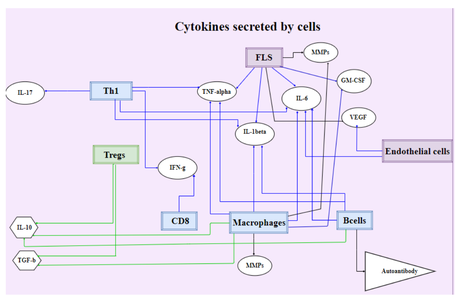

Fig 2.1a : Cytokine secretion

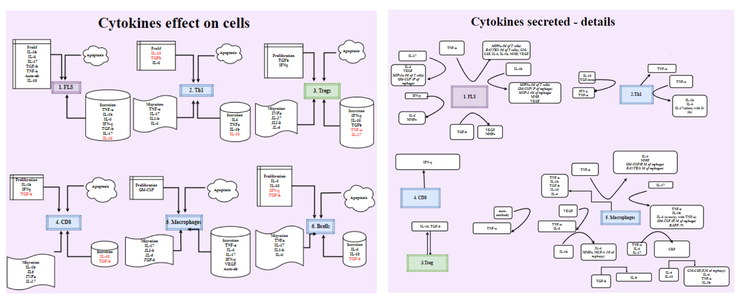

Fig 2.1b, 2.1c : effect of cytokines on cellular functions

Fig 2.1: The network of interactions in the synovium can be classified into A) Cytokine secretion network by cells (Fig 2.1a) B) Cytokines affecting the cell cycle (Fig 2.1b) C) Regulation of cytokine secretion by other cytokine (Fig 2.1c)

Pathways affected by therapies

Methotrexate (MTX) is an immune system suppressant used in RA to reduce inflammation

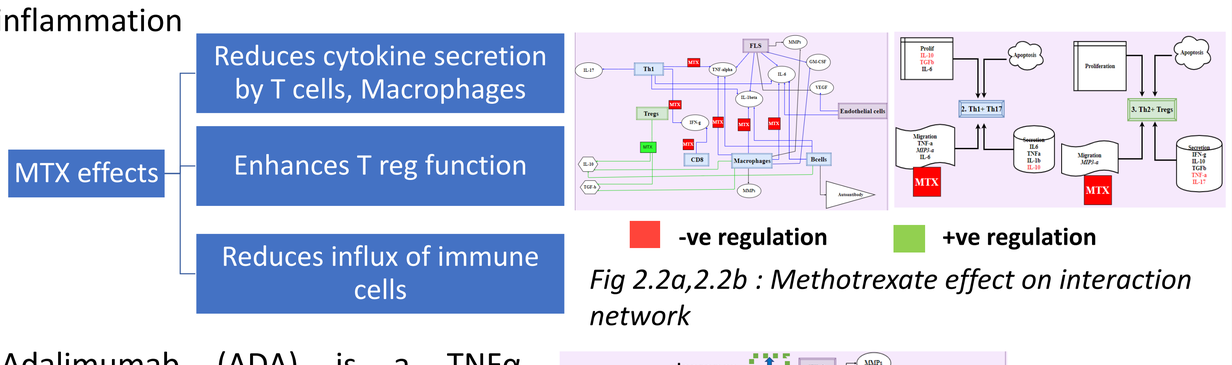

Fig 2.2a,2.2b : Methotrexate effect on interaction network

Adalimumab (ADA) is a TNFα antagonist used to reduce the activity of TNFα in the synovium

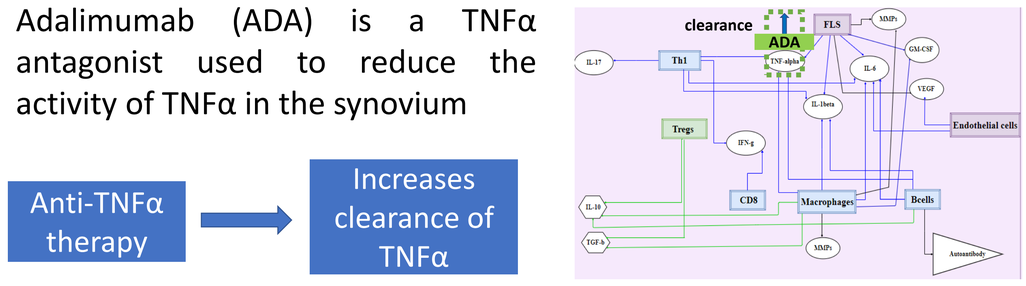

Fig 2.3 : Adalimumab effect on interaction network

3. Data for model calibration: Top down and Bottom up data

Cell type	Cytokines	P/M/A/S	Description/ comments	Reference
FLS	IL-6	Secretion	Causes secretion of MMPs by FLS	Yoshida et al, 2014
	IL-6	Secretion	VEGF	Nakahara et al, Arthritis Rheum. 2003
	IL-6	Proliferation	causes proliferation of FLS	Yoshida et al, 2014
	TNF -alpha	Proliferation	causes proliferation of FLS	Kobayashi et al, Arthrities & Rheumatism, 1999
	TNF-alpha	Apoptosis	Induces apoptosis (in absence of IFNg)	Firestein et al, Journal of Clinical Investigation 1995

Table 3.1 : Bottom up dashboard (Qualitative)

Parameter Name	Description	Mean value	Min value	Max value	Units	Primary Reference	Reliability score
kg_FLS_Baseline	Baseline proliferation rate of FLS	0.275	0.197	0.369	proliferation rate per day	Tolboom et al, Ann Rheum Dis, 2002	High
kd_FLS_Baseline	Apoptosis rate of FLS	3	2	4	% Apoptosis	Firestein et al, J Clin Invest. 1995	High
kp_MMP	secretion rate of MMPs by FLS	1400	1232	1568	ng/ml	Chabaud et al, Cytokines, 2000	High
kg_Endo_Baseline	Baseline proliferation rate of EC		2500	9700	cells/well	Seghazzi et al, JCB, 1999	Medium
kcl_IL6	clearance rate of IL6	3	2	4	hours	Marino et al.Nephrology Dialysis Transplantation, 2007	High

Table 3.2 : Bottom up dashboard (Quantitative)

Type of cells	Mean/Median	Lower bound	Upper bound	Units	Reference 1
Fibrocytes Like Synoviocytes (FLS)	441	35	2405	cells/mm2	Krann et al, Ann Rheum Dis. 2004
T cells (all CD3+)	480	137	2013	cells/mm2	Krann et al, Ann Rheum Dis. 2004
CD4	403	2	1702	cells/mm2	Thurlings et al, Ann Rheum Dis. 2008
Th1	61	18	71	% expression	Villa et al, PLOS, 2012
Th17	2.19	0.84	5.02	% expression	Villa et al, PLOS, 2013
Th2	0.3		0.6	% expression	Isomaki et al, Immunoloy, 1999
Treg	19.6	15.2	24	%	Jiao et al, SJR,2007

Table 3.3 : Ranges of cell numbers in synovial tissue taken from the biopsies of RA patients

A snapshot from 'Bottom up' data tables. Table 3.1 shows effects of cytokines on cell functions. Table 3.2 shows the tabulated parameter values, their ranges and sources. Table 3.3 shows the range of cell densities observed in RA patients

Name of Trial	Patient selection criterion
Premier Study, 2006[3]	MTX naive
RA BEAM trial, 2017[4]	Inadequate response to MTX (>=12weeks of MTX)

Table 3.4 : 'Top-down data'. Clinical trials used for calibrating the model.

4. Model simulations

The two treatments of interest are Methotrexate (MTX) and Anti-TNFα therapy Adalimumab (ADA). The dosing regimen for MTX is 20 mg Q1w and for ADA is 40 mg Q2w. PK model and parameters are taken from literature. The model is calibrated initially to match the behaviour of a representative patient, such a virtual subject is called 'Reference Virtual Subject'.

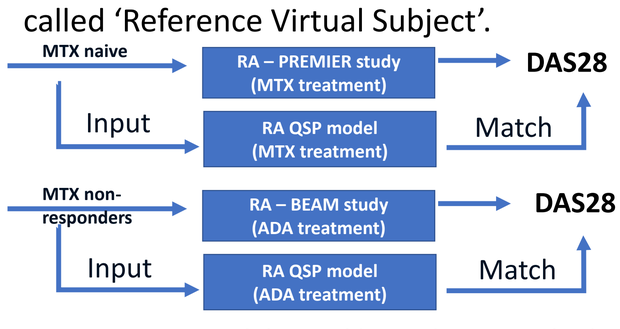

Fig 4.1: QSP model is calibrated to match the outcomes from selected clinical trials

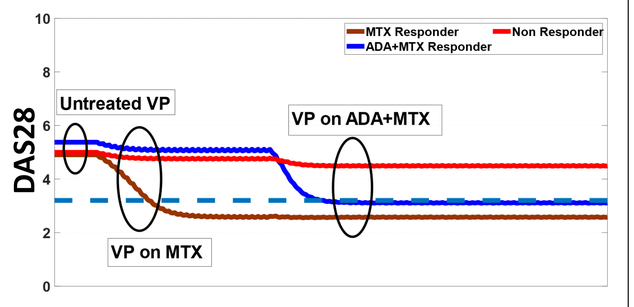

Fig 4.2: Simulation of virtual subjects with different responses to therapies

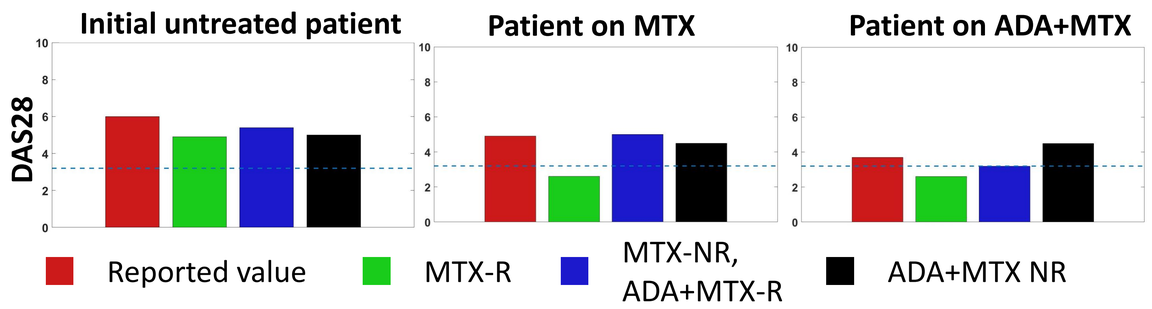

Fig 4.3: DAS28 values for the reported average patient and simulated virtual subjects

5. Future directions

- Next step is to create a Virtual Population to match clinical data for MTX and ADA therapies. Model validation will be performed using a previously uncalibrated therapy such as anti-IL6.
- Model can be expanded to include therapeutic pathways such as anti-IL6, anti-IL17, JAK inhibitor.
- The model can also be repurposed to other auto-immune diseases.

	RA (Joint), Current model	IBD (Gut)	Psoriasis (Skin)
Key Immune cells	Macrophages, B cells, Th1, Th17, Tregs, CD8+	Th1, Th2, Th17, Tregs, NK cells, PMNs, Dendritic cells, CD8+	Langerhans cells, Dendritic cells, PMNs, Th17, Th1, Tregs, CD8+, Macrophages
Clinical manifestations	Bone and cartilage destruction	Loss of barrier function	Increase in epidermal thickness
Disease scores	DAS28, ACR	CDAI/MAYO score	PASI

Table 5.1: A modelling view of different Auto-Immune conditions

6. References

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