Rheumatoid Arthritis

CONTENTS

Executive Summary

Rheumatoid arthritis is a chronic inflammatory disease. This project presents a mathematical model of rheumatoid arthritis with two compartments, namely lymph node and synovium. The model structure remains the same for healthy and diseased simulations, with one parameter varied to differentiate healthy and diseased. The clinical biomarkers such as C-Reactive protein, Rheumatoid Factor, and DAS score are correlated with the model enabling the prediction of dosage regimes by PKPD for experimental drugs. A two-compartmental pharmacokinetic model is used to describe the serum drug concentration-time data.

OBJECTIVES

The objectives of the project are listed below:

- To understand the pathophysiology of rheumatoid arthritis and build a mathematical model based on the ordinary differential equation to capture the biological aspects of the disease.
- To benchmark the model parameters to match the dynamics of each species in the model and relate it with the clinical outcomes.
- To perform sensitivity analysis to get the most sensitive parameters in the model.
- To create a virtual population representing the variations across the individuals.
- To model the pharmacokinetics and link it to the model to get the pharmacodynamics.
- To understand the genetic modifications (SNPs) responsible for the disease.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory autoimmune disease associated with articular, extra-articular, and systemic effects. It has been reported that RA affects ~0.5-1% of the adult population of developed regions[1]. RA is characterized by inflammation of synovium and swelling, autoantibody production, cartilage and bone destruction, and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders. ACPAs can be detected in approximately 67% of RA patients and serve as a useful diagnostic reference for patients with early, undifferentiated arthritis and indicate likely disease progression to RA[2]. Citrullination is the post-translational modification of arginine into citrulline by peptidyl arginine deiminases (PAD). Variable citrullinated autoantigens recognized by ACPA include keratin, filaggrin, fibrin/fibrinogen, vimentin, type II collagen, cartilage oligomeric matrix protein (COMP), and α-enolase, have been identified in RA[3]. This post-translational modification occurs under both physiological and pathological circumstances.

Treatment was mainly by the pyramid approach, which initiated rest in bed, nonsteroidal anti-inflammatory drugs (NSAIDs), and disease modifying antirheumatic drugs (DMARDs) therapy that usually led to disease exacerbation. Moreover, a new generation of biological treatments, monoclonal antibodies (mAbs), intends to decrease immune system hyperactivation and alleviate the inflammatory manifestations. Biological DMARDs are a group of drugs that target specific molecules or molecular pathways involved in RA inflammatory processes.

A combination of genetic, epigenetic, and environmental factors is responsible for the onset and development of RA. An array of susceptible genes (human leukocyte antigen (HLA) class II and more than 100 susceptibility loci including PTPN22, PADI4, TRAF1, and CTLA4), nongenetic factors (sex hormones, smoking, periodontal infection, and microbiota), immune (macrophages, dendritic cells, mast cells, neutrophils, T cells, and B cells) and nonimmune (fibroblasts and chondrocytes) cells, and inflammatory mediators (autoantibodies, cytokines, chemokines, and proteases) are collectively involved in the inflammatory processes targeting the cartilage and bone effectuating functional loss of joints[4].

MODEL DESCRIPTION

We developed and analyzed the mathematical model of rheumatoid arthritis based on the current literature data on the dynamics of the disease, including the Th cells and the cytokine levels in the healthy and diseased state. The model includes 23 differential equations.

In healthy conditions, the T-cell differentiation favours the production of T-reg cells, which produces TGFβ, which is anti-inflammatory, as shown in Figure 1.

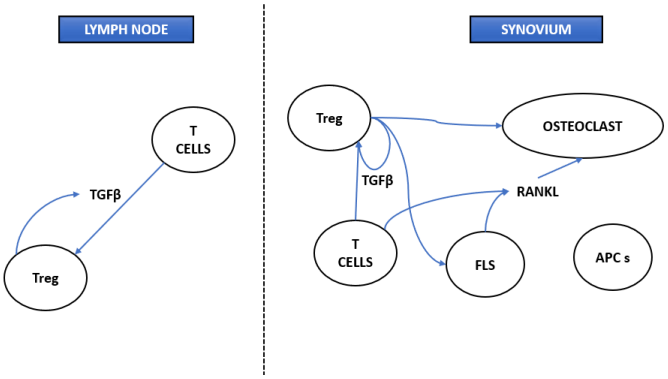


Figure 1: Schematic representation of the model for a healthy patient.

The pathology of rheumatoid can be due to various genetic and environmental factors. Chronic inflammation causes citrullination, which activates the antigen-presenting cells. The activated APCs migrate to the lymphoid organs to activate T-cells, which in turn activate the B-cells. The activated T-cells will be differentiated into Th2, Th17 cells. Thus, leading to reduced T-reg production. The Th2 cells interact with B-cells leading to the production of autoantibodies. IL6 mainly induces the Th17 differentiation. IL6 and TNFα inhibit the T-reg production. The T-cells, T-reg, Th17, and autoantibodies migrate from the lymph node to the synovium. In the synovium, a similar mechanism of T-cell differentiation happens. In the synovium, the IL17 produced by the Th17 cells stimulates the production of pro-inflammatory cytokines. FLS present in the synovial membrane plays a significant role in RA pathogenesis by causing the destruction of cartilage through osteoclast proliferation via RANKL and increasing the inflammatory immune response by producing more IL6. The schematic representation of the diseased condition model is shown in Figure 2.

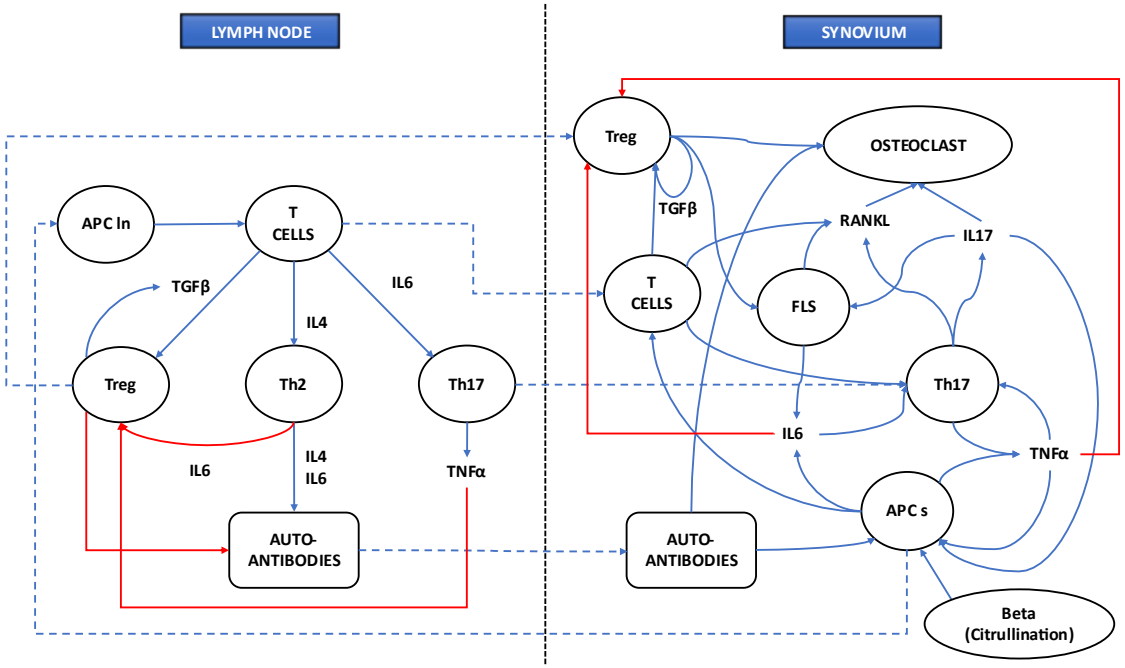


Figure 2: Schematic representation of the model for a rheumatoid arthritis patient.

EQUATIONS OF THE MODEL

Rheumatoid arthritis is modeled using ordinary differential equations as follows,

EQUATIONS IN THE SYNOVIUM

THE EQUATION FOR APC IN THE SYNOVIUM:

The inflammation of the joints or environmental or genetic risk factors may lead to the citrullination of proteins in the joint. These citrullinated proteins activate the Antigen Presenting Cells (APC) in the synovium.

$$\frac{d[APC]_S}{dt} = -(k_{n1} + beta).k.[APC]_S + k_s - k_d[APC]_S$$

Where $beta$ is the function of citrullination. In a healthy case, beta is set to zero. In diseased cases, beta is greater than zero and can be varied to simulate the desired severity of the disease.

THE EQUATION FOR APC ACTIVATED IN THE SYNOVIUM:

Citrullination induces the activation of APC in the synovium. Autoantibodies, TNFα, and IL17 enhance the proliferation of activated APC.

$$\frac{d[APC^*]_S}{dt} = (k_{n1} + beta).k.[APC]_S - k_{36}[APC^*]_S + k_{35}[APC^*]_S \frac{[AA]_S^2}{{k'^2}_{35} + [AA]_S^2} + k_{44}[APC^*]_S \frac{[TNFa]_S^2}{{k'^2}_{44} + [TNFa]_S^2} + k_{23}[APC^*]_S \frac{[IL17]_S^2}{{k'^2}_{23} + [IL17]_S^2} - k_{20}[APC^*]_S$$

THE EQUATION FOR T-CELLS IN THE SYNOVIUM:

$$\frac{d[Tcell]_S}{dt} = k_{s2} - k_{d2}[Tcell]_S - k_{54}[Tcell]_S - k_3[Tcell]_S \left(\frac{k_{48}}{k_{48} + [IL6]_S}\right)\left(\frac{k_{52}}{k_{52} + [TNFa]_S}\right) + k_{t1}[Tcell]_{LN}$$

THE EQUATION FOR TH17 CELLS IN THE SYNOVIUM:

The differentiation of T-cells produces the Th17 cells. IL6 induced the proliferation of Th17 cells and activated APC provides the co-stimulation of T-cells. The drug Abatacept blocks the Tcell co-stimulation, and the drug tocilizumab blocks the receptor IL6.

$$\frac{d[Th_{17}]_S}{dt} = \left(\frac{k_{costim_1}}{k_{costim_1} + Drug_{tcell_{costim}}}\right)\left(k_{54}[Tcell]_S - k_{47}[Th_{17}]_S + \left(\frac{k_{il6_1}}{k_{il6_1} + Drug_{il6_{Rec}}}\right)k_{46}[Th_{17}]_S[APC^*]_S\left(\frac{[IL6]_S^2}{{k'^2}_{46} + [IL6]_S^2}\right)\right) + k_{t4}[Th_{17}]_{LN}$$

The equation for Treg cells in the synovium:

Treg cells are differentiated from T-cells. TGFβ enhances the proliferation of Treg cells. IL6 and TNFα inhibit the differentiation and proliferation of Treg cells. The drug tocilizumab inhibits the IL6 receptors.

$$\frac{d[Treg]_S}{dt} = \left(k_3[Tcell]_S + k_{n6}\,[Treg]_S \left(\frac{[TFGB]_S^2}{k'^2{}_3 + [TGFB]^2{}_S} \right) \right) \left(\frac{\left(1 + \frac{Drug_{il6_{Rec}}}{k_{il6_2}}\right) k_{48}}{k_{48} + [IL6]_S} \right) \left(\frac{k_{52}}{k_{52} + [TNFa]_S} \right) - k_{13}[Treg]_S + k_{t2}[Treg]_{LN}$$

The equation for TGFb in the synovium:

TGFβ is produced by Treg cells.

$$\frac{d[TGFB]_S}{dt} = k_4[Treg]_S - k_{10}[TGFB]_S$$

The equation for IL6 in the synovium:

IL6 is produced by activated APC and FLS.

$$\frac{d[IL6]_S}{dt} = k_{50}[APC^*]_S + k_{66}[FLS] - k_{49}[IL6]_S$$

The equation for IL17 in the synovium:

IL17 is produced in some basal concentrations, and it is enhanced by Th17 cells.

$$\frac{d[IL17]_S}{dt} = k_{55}\left(k_{n2} + \left(k_{n3} \left(\frac{[Th17]_S^2}{k_{55}'^2 + [Th17]_S^2} \right) \right) \right) - k_{56}[IL17]_S$$

The equation for TNFa in the synovium:

TNFα is produced by Th17 cells, APCs. The drug infliximab blocks the production of TNFα.

$$\frac{d[TNFa]_S}{dt} = k_{64}[Th17]_S + k_{74}[APC^*]_S - k_{45}[TNFa]_S - Drug_{tnf}[TNFa]_S$$

The equation for Autoantibodies in the synovium:

The autoantibodies in the synovium is the result of translocation of autoantibodies from the lymph node.

$$\frac{d[AA]_S}{dt} = k_{t3}[AA]_{LN} - k_{38}[AA]_S$$

THE EQUATION FOR OSTEOCLAST:

TGFβ, RANKL, IL17, and autoantibodies enhance the proliferation of osteoclasts.

$$\frac{d[OC]_S}{dt} = k_{s3} + k_5[OC]_S \frac{[TFGB]_S^2}{k'^2{}_5 + [TGFB]_S^2} + k_8[OC]_S \frac{[RANKL]_S^2}{k'^2{}_8 + [RANKL]_S^2} + k_{57}[OC]_S \frac{[IL17]_S^2}{k'^2{}_{57} + [IL17]_S^2} + k_{71}[OC]_S \frac{[AA]_S^2}{k'^2{}_{71} + [AA]_S^2} - k_{62}[OC]_S$$

THE EQUATION FOR FIBROBLAST LIKE SYNOVIOCYTES:

TGFβ and IL17 enhance the proliferation of FLS.

$$\frac{d[FLS]_S}{dt} = k_{s4} + k_9[FLS]_S \frac{[TFGB]_S^2}{k'^2{}_9 + [TGFB]_S^2} + k_{58}[FLS]_S \frac{[IL17]_S^2}{k'^2{}_{58} + [IL17]_S^2} - k_{61}[FLS]_S$$

THE EQUATION FOR RANKL:

FLS produces RANKL and it is enhanced by the Th17 cells. The T-cells also produce RANKL.

$$\frac{d[RANKL]_S}{dt} = k_7[FLS]_S \left(k_{n4} + \frac{[Th17]_S^2}{k_7'^2 + [Th17]_S^2}\right) + k_{73}[Tcell]_S - k_{11}[RANKL]_S$$

THE EQUATION IN THE LYMPH NODE

THE EQUATION FOR APC ACTIVATED IN THE LYMPH NODE:

The activated APC from the synovium gets translocated to the lymph node.

$$\frac{d[APC^*]_{LN}}{dt} = k_{20}[APC^*]_S - k_{22}[APC^*]_{LN}$$

THE EQUATION FOR T-CELLS IN THE LYMPH NODE:

$$\frac{d[Tcell]_{LN}}{dt} = k_{sTcell} - k_{dTcell}[Tcell]_{LN} - k_1[Tcell]_{LN}\left(\frac{k_{34}}{k_{34} + [IL6]_{LN}}\right)\left(\frac{k_{29}}{k_{29} + [TNFa]_{LN}}\right) - k_{24}[Tcell]_{LN} - k_{26}[Tcell]_{LN} - k_{t1}[Tcell]_{LN}$$

THE EQUATION FOR TREG CELLS IN THE LYMPH NODE:

A similar mechanism for Treg cells mentioned in the synovium happens in the lymph node.

$$\frac{d[Treg]_{LN}}{dt} = \left(k_1[Tcell]_{LN} + k_p[Treg]_{LN}\frac{[TGFB]_{LN}^2}{k'^2{}_1 + [TGFB]_{LN}^2}\right)\left(\frac{\left(1 + \frac{Drug_{il6_{Rec}}}{k_{il6_3}}\right)k_{34}}{k_{34} + [IL6]_{LN}}\right)\left(\frac{k_{29}}{k_{29} + [TNFa]_{LN}}\right) - k_{16}[Treg]_{LN} - k_{t2}[Treg]_{LN}$$

THE EQUATION FOR TH2 CELLS IN THE LYMPH NODE:

The differentiation of T-cells produces the Th2 cells. IL4 induces the proliferation of Th17 cells and activated APC provides the co-stimulation of T-cells. The drug Abatacept blocks the T-cell co-stimulation.

$$\frac{d[Th2]_{LN}}{dt} = \left(\frac{k_{costim_2}}{k_{costim_2} + Drug_{tcell_{costim}}}\right)\left(k_{24}[Tcell]_{LN} + k_{th2pro}[APC^*]_{LN}[Th2]_{LN}\frac{[IL4]^2_{LN}}{k'^2_{24} + [IL4]^2_{LN}}\right) - k_{25}[Th2]_{LN}$$

THE EQUATION FOR TH17 CELLS IN THE LYMPH NODE:

A similar mechanism for Th17 cells mentioned in the synovium happens in the lymph node.

$$\frac{d[Th17]_{LN}}{dt} = \left(\frac{k_{costim_3}}{k_{costim_3} + Drug_{tcell_{costim}}}\right)\left(k_{26}[Tcell]_{LN} + \left(\frac{k_{il6_4}}{k_{il6_4} + Drug_{il6_{Rec}}}\right)k_{th17pro}[APC^*]_{LN}\frac{[IL6]^2_{LN}}{k'^2_{26} + [IL6]^2_{LN}}\right) - k_{27}[Th17]_{LN} - k_{t4}[Th_{17}]_{LN}$$

THE EQUATION FOR TNFA IN THE LYMPH NODE:

$$\frac{d[TNFa]_{LN}}{dt} = k_{s5} + k_{28}[Th17]_{LN} - k_{30}[TNFa]_{LN} - Drug_{tnf}[TNFa]_{LN}$$

THE EQUATION FOR AUTOANTIBODIES IN THE LYMPH NODE:

IL4 and IL6 induce the Th2 cells to produce autoantibodies in the lymph node, and TGFβ inhibits the production of autoantibodies. The drug tocilizumab blocks the receptors of IL6, thereby reducing the autoantibody production.

$$\frac{d[AA]_{LN}}{dt} = \left(\frac{k_{il6_5}}{k_{il6_5} + Drug_{il6_{Rec}}}\right)k_{31}[Th2]_{LN}\frac{[IL4]_{LN}}{k'_{31} + [IL4]_{LN}}\frac{[IL6]_{LN}}{k''_{31} + [IL6]_{LN}}\left(\frac{k_{33}}{k_{33} + [TGFB]_{LN}}\right) - k_{32}[AA]_{LN} - k_{t3}[AA]_{LN}$$

THE EQUATION FOR TGFB IN THE LYMPH NODE:

TGFβ in the lymph node is produced by Treg cells in the lymph node.

$$\frac{d[TGFB]_{LN}}{dt} = k_2[Treg]_{LN} - k_{14}[TGFB]_{LN}$$

THE EQUATION FOR IL4 IN THE LYMPH NODE:

IL4 in the lymph node is produced in basal concentration, and it is enhanced by Th2 cells.

$$\frac{d[IL4]_{LN}}{dt} = k_{67}\left(k_{s6} + k_{n5}\left(\frac{[Th2]_{LN}^2}{k_{67}'^2 + [Th2]_{LN}^2}\right)\right) - k_{68}[IL4]_{LN}$$

THE EQUATION FOR IL6 IN THE LYMPH NODE:

IL6 in the lymph node is produced by Th2 cells in the lymph node.

$$\frac{d[IL6]_{LN}}{dt} = k_{69}[Th2]_{LN} - k_{70}[IL6]_{LN}$$

BENCHMARKING

The data for each species is collected from literature as listed in Table 1. From this data, the fold change between healthy and diseased states is obtained. These fold change values are benchmarked in the model. The benchmarking was done manually for this model.

Table 1: Fold change values used to benchmark the model

	Species	Healthy	Diseased	Ref	Expected Fold Change	Observed Fold Change
Lymph Node	IL4 (pg/mL)	4	6	[5]	1.5	2.18
	IL6 (pg/mL)	800	2400	[6]	3	3.22
	Autoantibodies (%)	12	78	[7]	6.5	8.97
	Th17 (no. of cells)	200	330	[8]	1.7	2.18
	Treg (%)	7	5.5	[9]	1.27	1.27
	TNFα (pg/mL)	750	2000	[6]	2.6	2.18
Synovium	IL6 (pg/mL)	100	400	[10]	4	3.84
	IL17 (pg/mL)	300	600	[10]	2	2.19

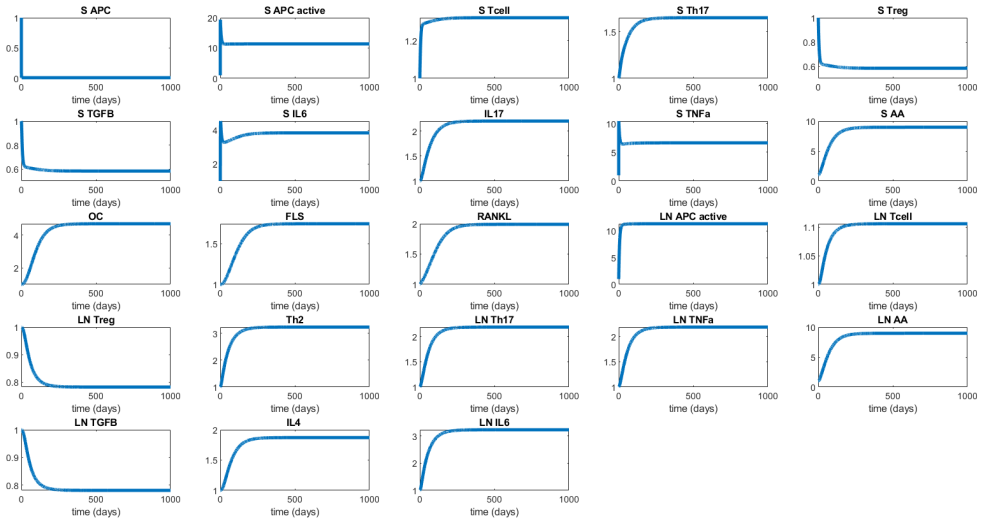


Figure 3: Benchmarked fold change for each species

BI-STABILITY PLOTS FOR EACH SPECIES

To check whether the model has two stable equilibrium states, bistability was analyzed for different beta values. Here we found that our model doesn't have two stable equilibrium states and is hence not bistable.

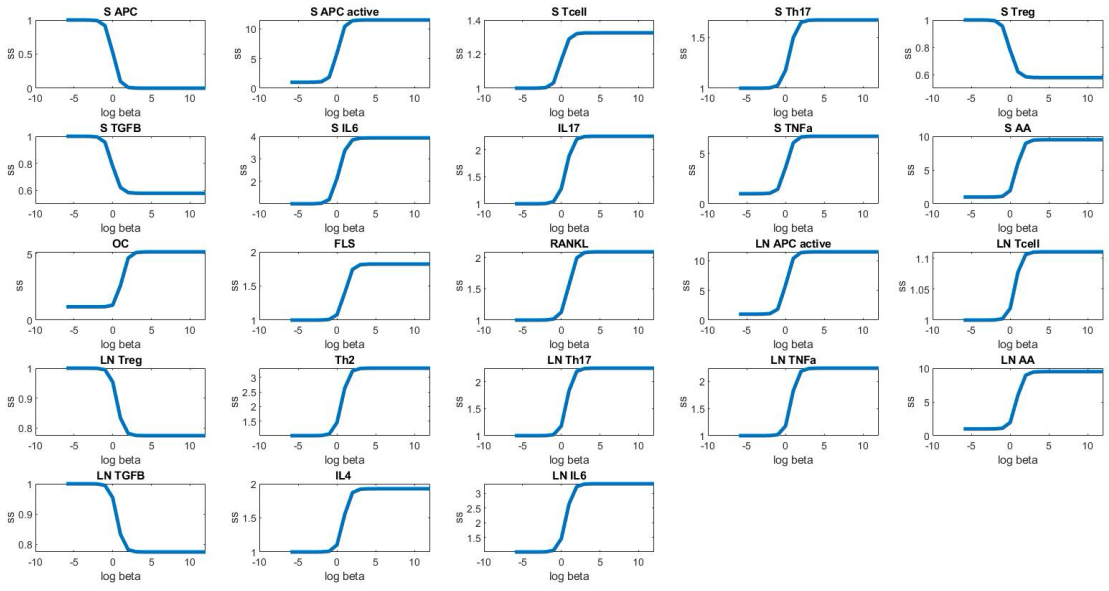


Figure 4: Bi-stability plot with respect to beta.

Clinical Outcomes

C-reactive protein (CRP)

The C-Reactive Protein (CRP) is the indicator of inflammation in the body. CRP production by the liver increases as the result of increased pro-inflammatory cytokines like IL6 and TNFα.

$$CRP = \frac{(13.7[IL6]_{LN} - 42) + (3.5[TNFa]_{LN} - 80.5)}{2}$$

Table 2: CRP value and its clinical significance[11]

C-reactive protein level (in mg/L of blood	Description
< 3	Healthy
3 – 10	Slightly elevated, e.g., pregnancy, the common cold, or gingivitis
10 – 100	Rheumatoid Arthritis, Crohn's Disease, or lupus
100 – 500	Inflammation of blood vessels
500 and above	Bacterial infection

Rheumatoid Factor (RF)

Rheumatoid factor is the autoantibody against the Fc region of IgG antibodies[12]. It is the most widely used blood test for the classification of rheumatoid arthritis.

$$RF = 0.866[AA]_{LN} - 2.6$$

Table 3: Rheumatoid Factor and its clinical significance[12]

RF (IU/mL)	Disease Activity
<25	Healthy
25-50	Low Disease Activity
50-100	Moderate Disease Activity
>100	High Disease Activity

DAS SCORE

The DAS score indicates the severity of rheumatoid arthritis in patients. It is calculated using the below formula[13].

$$DAS28(CRP) = 0.56\sqrt{28TJC} + 0.28\sqrt{28SJC} + 0.36\ln(CRP + 1) + 0.014PtGA + 0.96$$

Since the above formula uses the physical joints affected, we have correlated with CRP as follows,

$$DAS = (0.0844 * CRP) + 0.96$$

Table 4: DAS score and its clinical significance[14]

Score	Disease Activity
DAS28 < 2.6:	Remission
DAS28 >= 2.6 and <= 3.2:	Low Disease Activity
DAS28 > 3.2 and <= 5.1:	Moderate Disease Activity
DAS28 > 5.1:	High Disease Activity

RA SCORE

RA score is a customized scoring developed here at Research to quantify the severity of rheumatoid arthritis. RA score can be calculated as follows,

$$RA\ score = \frac{CRP + 2RF}{3}$$

Table 5: RA score and its clinical significance

Severity	RA Score
Healthy	< 17.66
Mild	17.66 – 36.66
Moderate	36.66 – 100
Critical	> 100

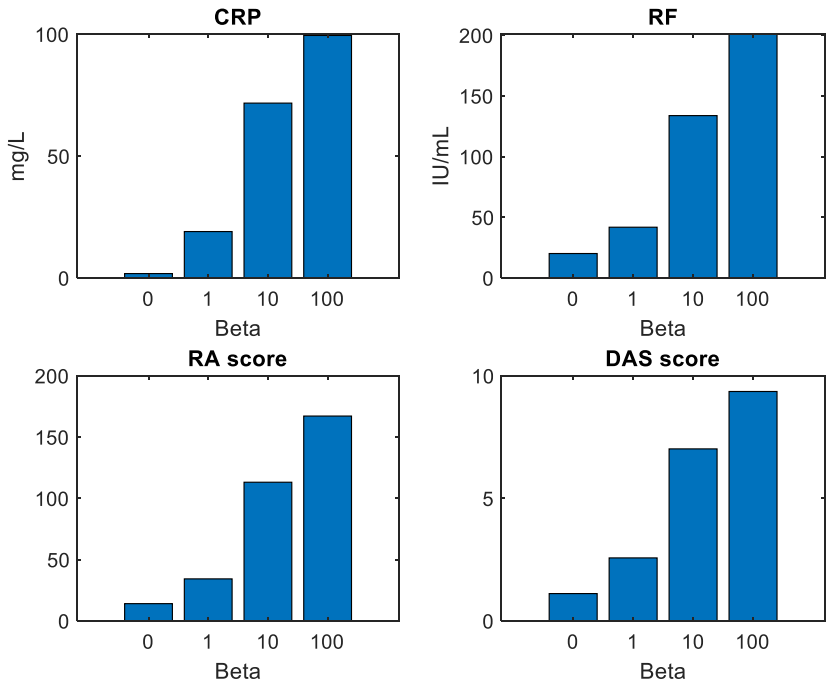


Figure 5: Clinical scores such as CRP, RF, RA score, and DAS score with respect to beta.

Sensitivity Analysis

To identify the critical reactions that affect the end clinical output, sensitivity analysis is done by varying a single parameter at a time by doubling and half the value. The parameters that resulted in maximum change in CRP and RF for minimum parameter change are taken as sensitive parameters. The sensitive parameters are listed in Table 6.

Table 6: Sensitive parameters in the model

Sensitive Parameters	Description
k_{24}	Basal Th2 production in lymph node from T-cells
k_{26}	Basal Th17 production in lymph node from T-cells
k_{28}	Production of TNFα by Th17 in lymph node
k_{20}	Activated APC translocation from synovium to lymph node
k_{th2pro}	Th2 proliferation by IL4 in lymph node
k_{35}	The proliferation of activated APC by Autoantibodies in the synovium
$k_{th17pro}$	Th17 proliferation by IL4 in lymph node
k_{69}	Production of IL6 by Th2 in lymph node
k_{44}	The proliferation of activated APC by TNFα in the synovium

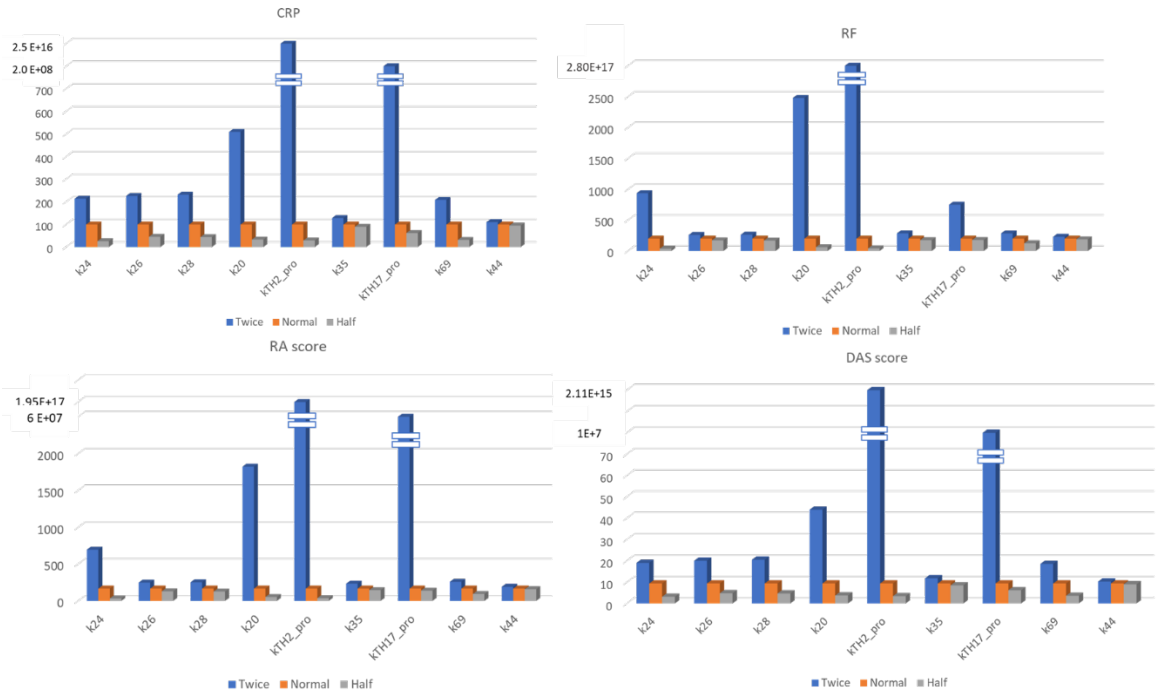


Figure 6: Bar plot showing the sensitive parameters varied twice and half.

POPULATION

For a fixed beta value, the sensitive parameters are varied randomly within a specific range to generate the population, as shown in Figure 7. In the population, each individual may fall into different levels of severity, as listed in Table 7.

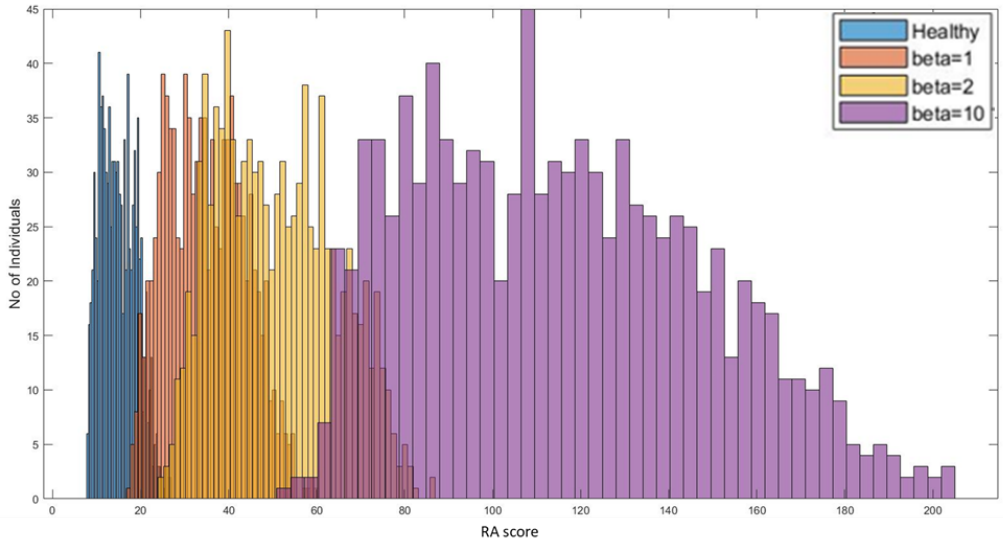
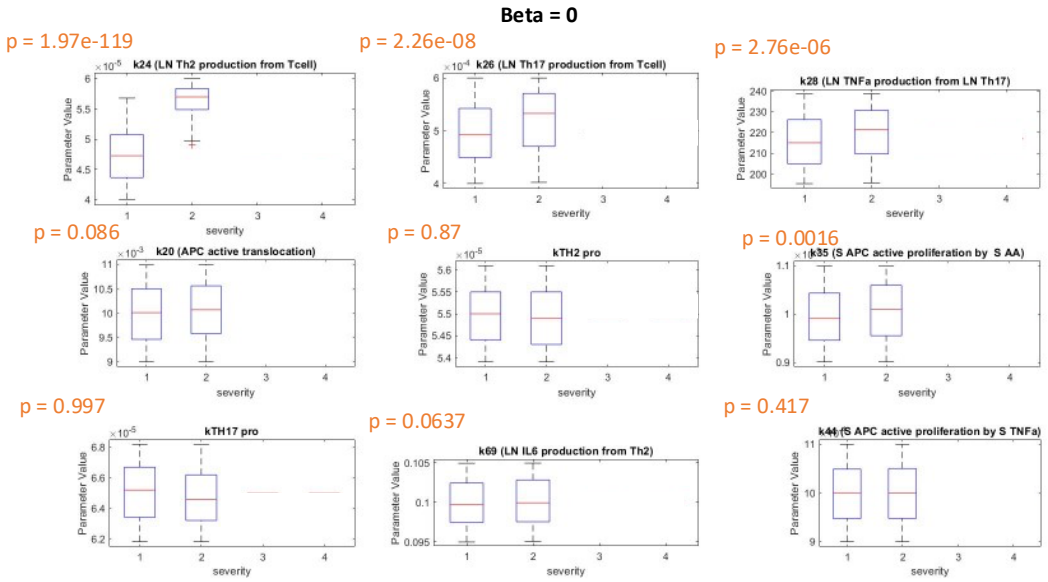


Figure 7: Population generated by varying the sensitive parameters for beta values 0, 1, 2, 10.

Table 7: Distribution of population across different levels of severity.

Beta	0	1	2	10
Healthy	71 %	1 %	0 %	0 %
Mild	29 %	58.1 %	16.6 %	0 %
Moderate	0 %	41.8 %	83.4 %	38.1 %
Critical	0 %	0 %	0 %	61.9 %



Wilcoxon rank sum test with significance of 0.05 left tailed

Figure 8: Box plot showing sensitive parameter range for different severity levels for a healthy population (beta=0).

To find the parameters that have a significant change in their values between different levels of severity, the Wilcoxon rank-sum test is performed with a significance of 0.05 and left tailed. A box plot shows ranges of various parameters in Figures 8 and 9. For beta = 0, the parameters k24, k26, k28, and k35 have a significant change in median. For beta=10, the parameters k24, k26, k20 and kth17_pro have significant change in median values.

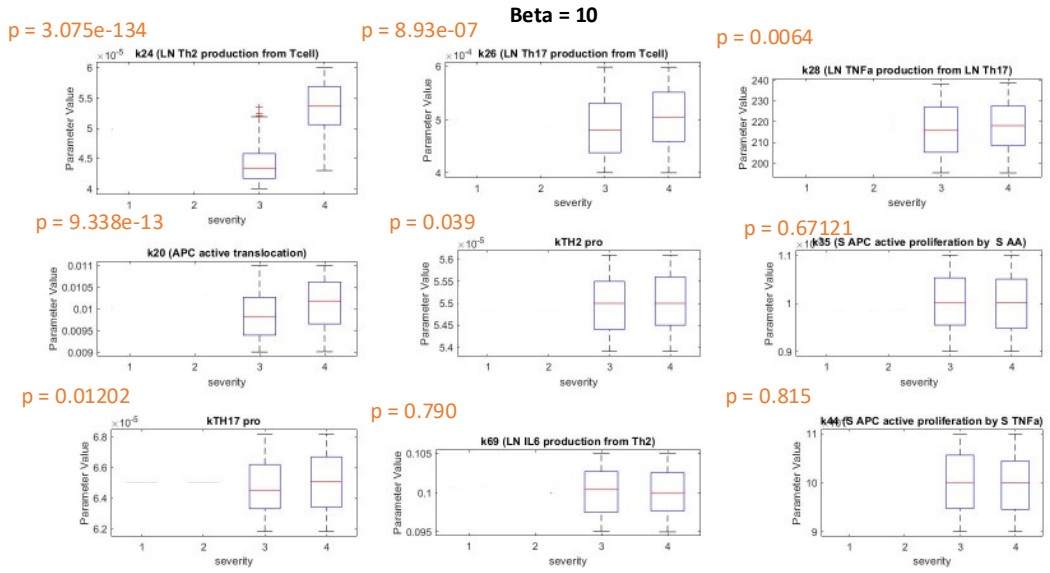


Figure 9: Box plot showing sensitive parameter range for different severity levels for a diseased population (beta=10).

PHARMACOKINETICS

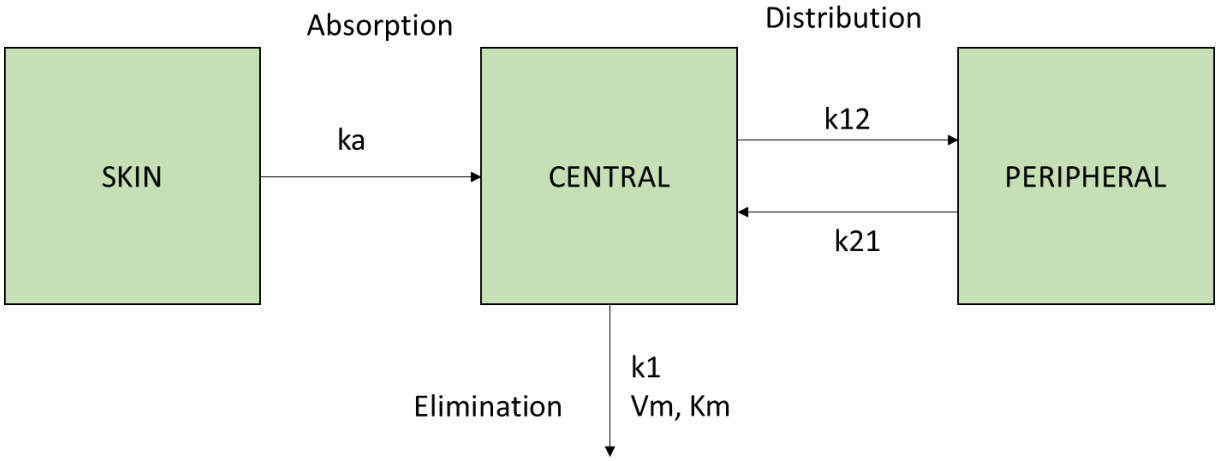


Figure 10: Schematics of two compartmental model with absorption.

$$\frac{dCentral}{dt} = -k_{drug}Central - \left(\frac{V_m}{V_{central}}\right)\left(\frac{Central}{k_m + Central}\right) + k_{21_{drug}}Drug - k_{12_{drug}}Central + f.k_a.Skin$$

$$\frac{dPeripheral}{dt} = -k_{21_{drug}}Drug + k_{12_{drug}}Central$$

$$\frac{dSkin}{dt} = -k_aSkin$$

Table 8: Two compartmental model parameters for the drugs Abatacept, Tocilizumab, Infliximab.

Parameter	Abatacept[15]	Tocilizumab[16]	Infliximab[17]
CL (L/day)	0.4896	0.3	0.456
Vc (L)	3.27	3.5	2.3
Q (L/day)	.636	0.2	4.32
Vp (L)	4.26	2.9	3.6
Ka (/day)	.0732	0.156	0
F	.805	0.745	0
Vm (mg/day)	0	7.5	0
Km (µg/mL)	0	2.7	0

ABATACEPT

Abatacept is one of the disease-modifying antirheumatic drugs (DMARD) used to treat moderate-to-severe rheumatoid arthritis. Abatacept is selective co-stimulation modulator. Here we have considered 125mg of drug administered as a subcutaneous injection every seven days for 200 days.

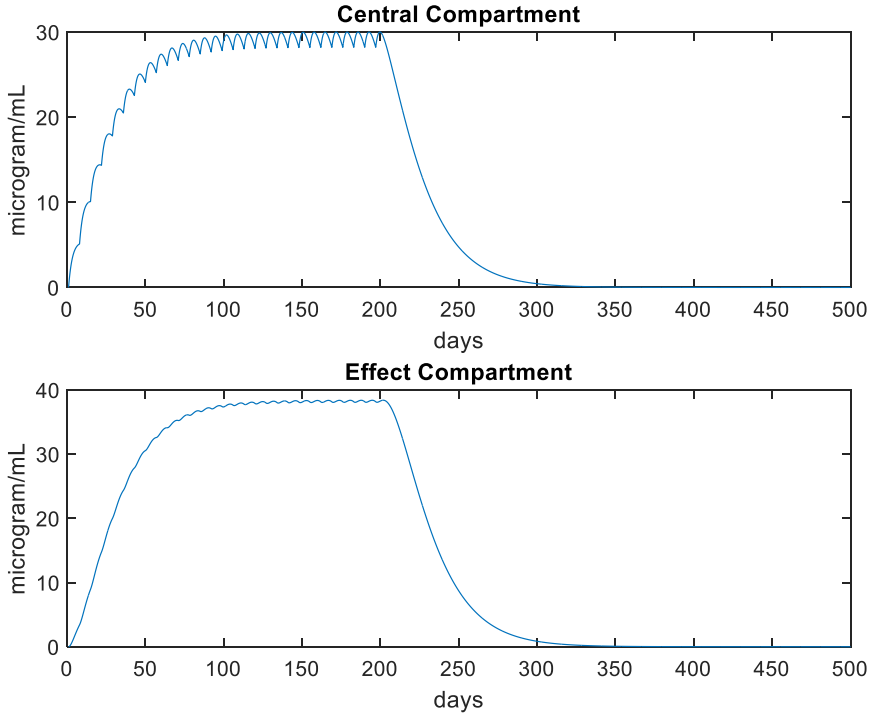


Figure 11: Simulated concentration of the drug Abatacept in the central and peripheral compartment.

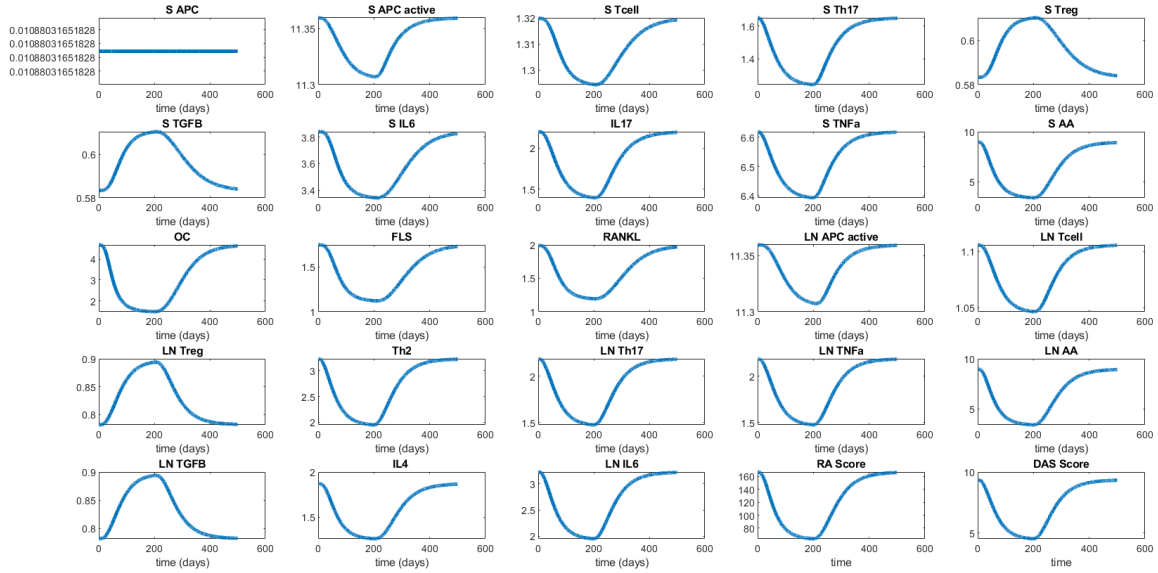


Figure 12: Effect of the drug Abatacept on each species in the model.

TOCILIZUMAB

Tocilizumab is an immune suppressive drug used to treat rheumatoid arthritis. It acts against the interleukin-6 receptor. Here we have considered 162mg of drug administered as a subcutaneous injection every 14 days for 200 days.

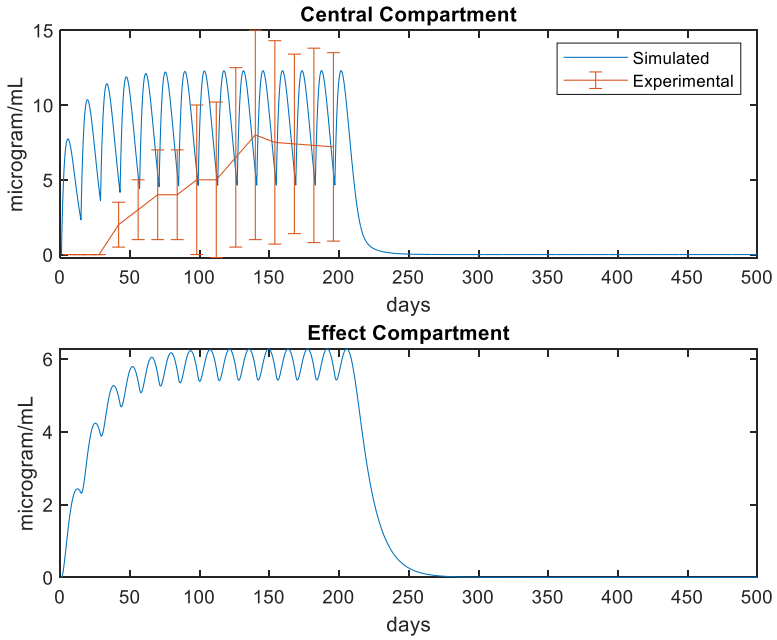


Figure 13: Simulated vs Experimental concentration of the drug tocilizumab in the central and peripheral compartment

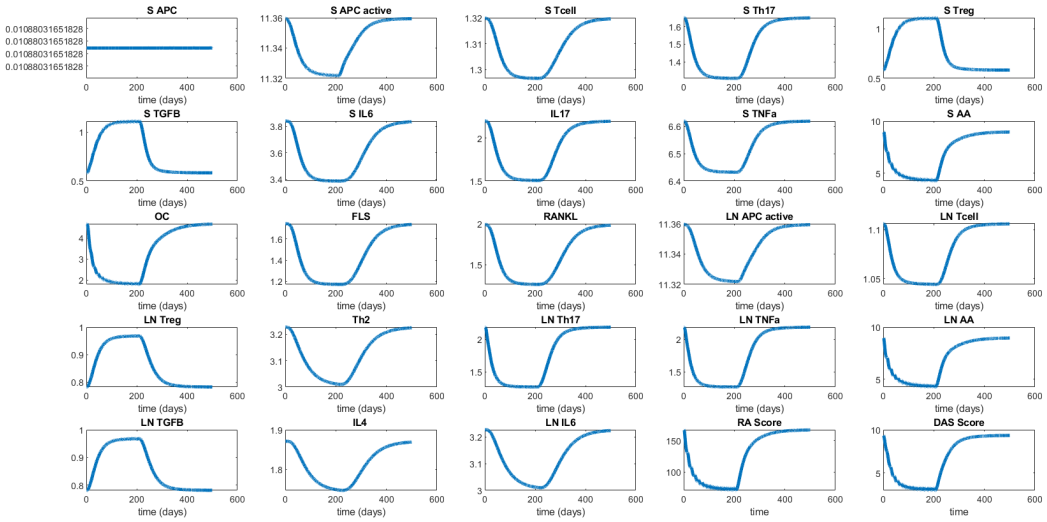


Figure 14: Effect of the drug tocilizumab on each species in the model.

INFLIXIMAB

Infliximab is a chimeric monoclonal antibody that works by blocking the TNFα. Here we have considered 3 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks for around 200 days.

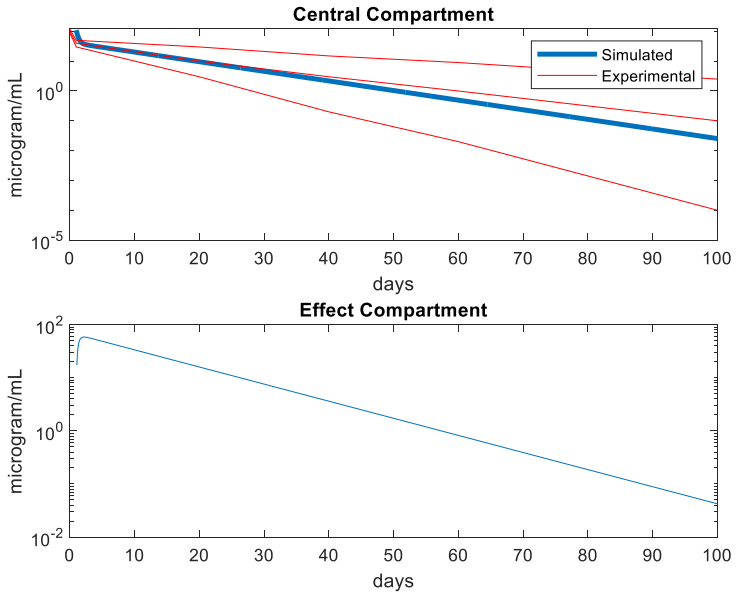


Figure 15: Simulated Vs Experimental concentration of the drug infliximab in the central and peripheral compartment for a single dose.

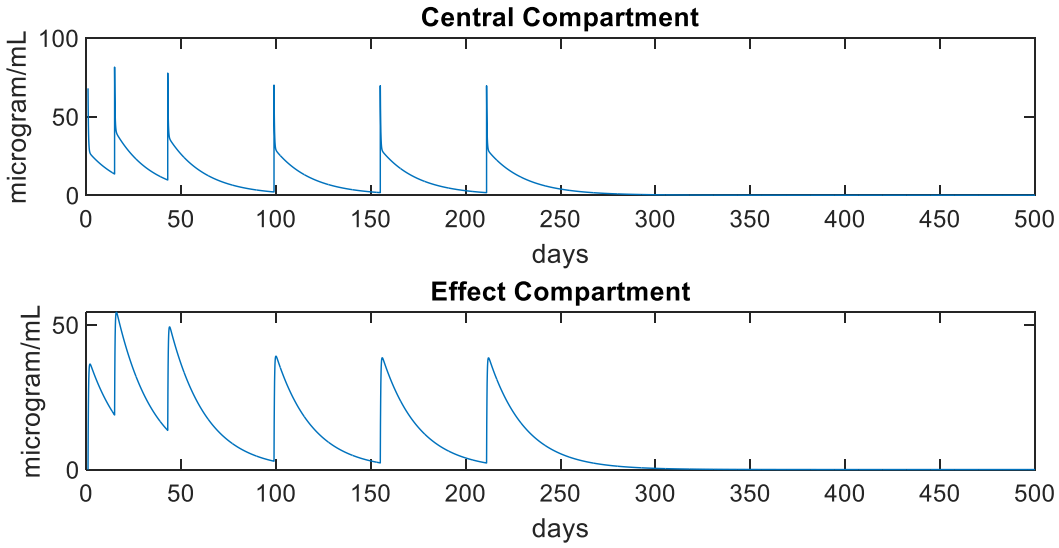


Figure 16: Simulated Concentration of the drug infliximab for multiple doses.

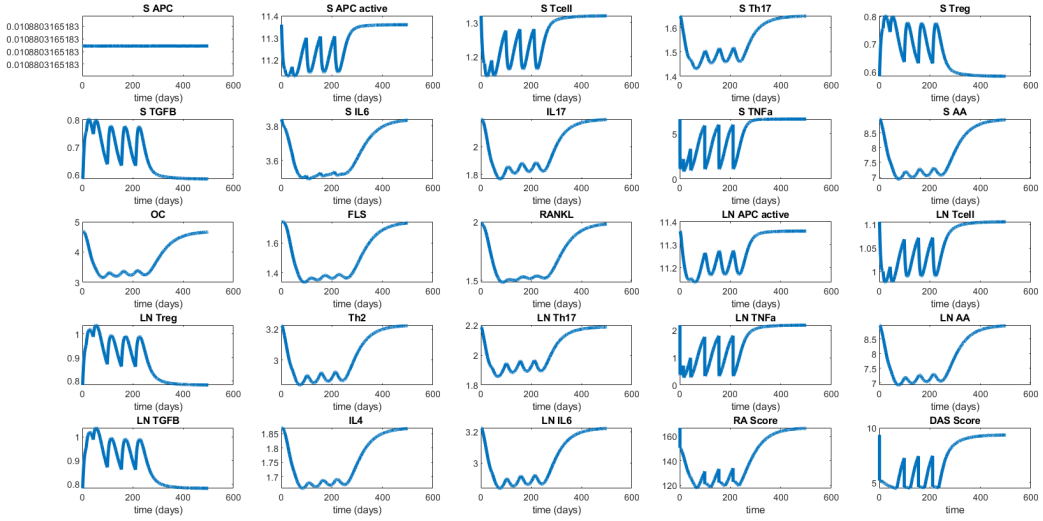


Figure 17: Effect of the drug infliximab on each species in the model.

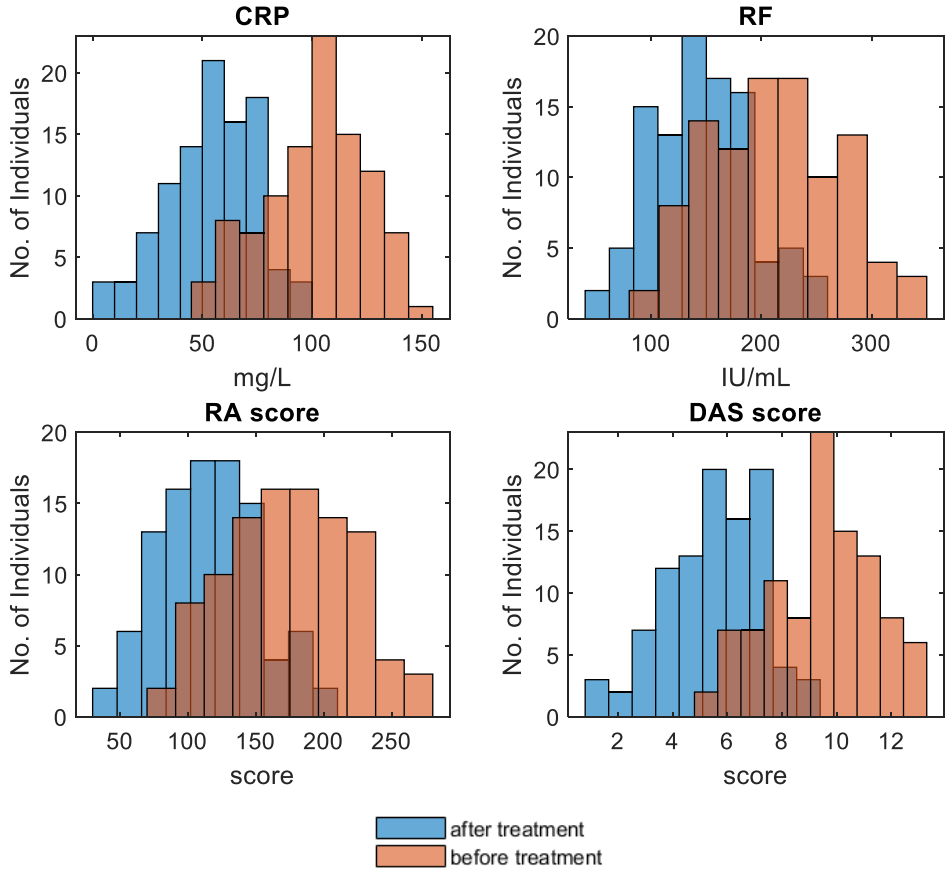


Figure 18: Population results for the clinical outcome before and after treatment with drug tocilizumab.

Table 9: Mean reduction in Clinical parameters after treatment with the drug tocilizumab

	Diseased (before treatment)		Diseased (after treatment)	
	Mean	SD	Mean	SD
CRP	101.06	23.03	53.84	20.90
RF	211	59.12	145.12	45.78
RA score	174.35	45.60	114.75	36.45
DAS score	9.49	1.94	5.5	1.76

GENOMICS

The SNPs which are responsible for rheumatoid arthritis are listed in Table 10. Based on the function for which each SNP is responsible, the corresponding parameters in the model are found. These SNPs parameters are varied to see how much each SNP is sensitive in rheumatoid arthritis, as shown in Figure 19.

Table 10: SNPs in Rheumatoid Arthritis

Gene	Parameters in the Model	Function	Ref.
HLA-DRB1	Kn1, k31	Macrophage polarization, RF factor	18,19
PTPN22	k24, k26 and k54	T-cell differentiation	20
TRAF1	k28, k69, k64, k74, k50 and k66	Inflammatory response and autoantibodies	21
CLA4	k3 and k1	Treg production disturbed	22–24
STAT4	k28, k64 and k74	TNFα	25
CCR6	k24, k26 and k54	T-cell differentiation	26
PADI4	kn1	Citrullination	27,28

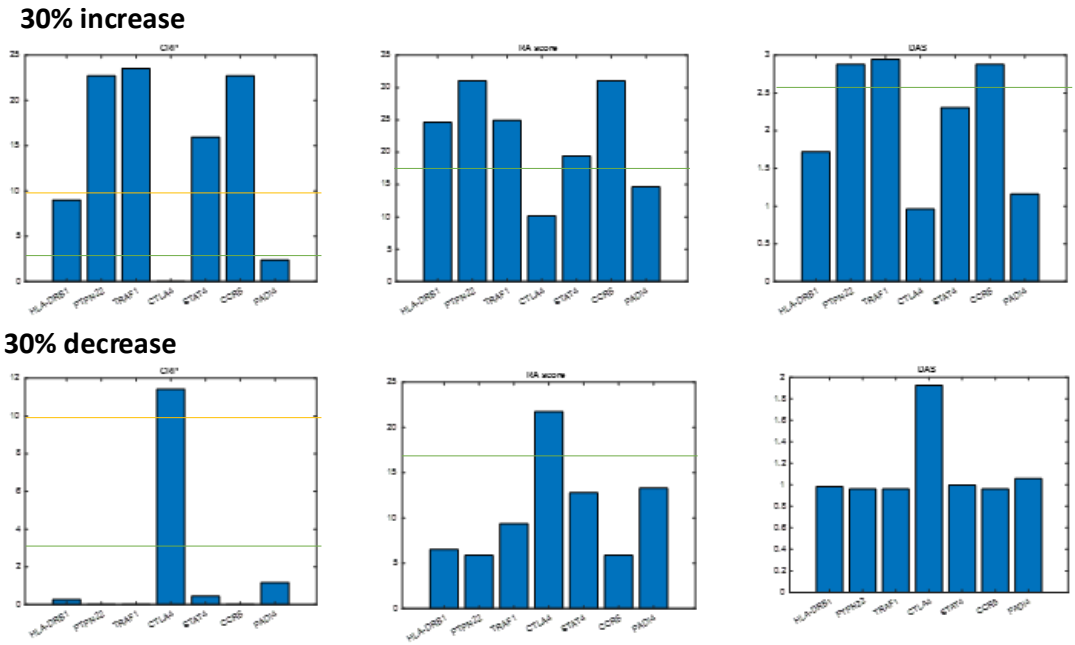


Figure 19: Variation of CRP, RA score and DAS score for increase/decrease in SNP.

ESTIMATING PARAMETER RANGE FOR CLINICAL BIOMARKERS

From the population data, for a CRP of 60 and RF value of 100, the corresponding ranges of each sensitive parameter are found and it is shown in Figure 20.

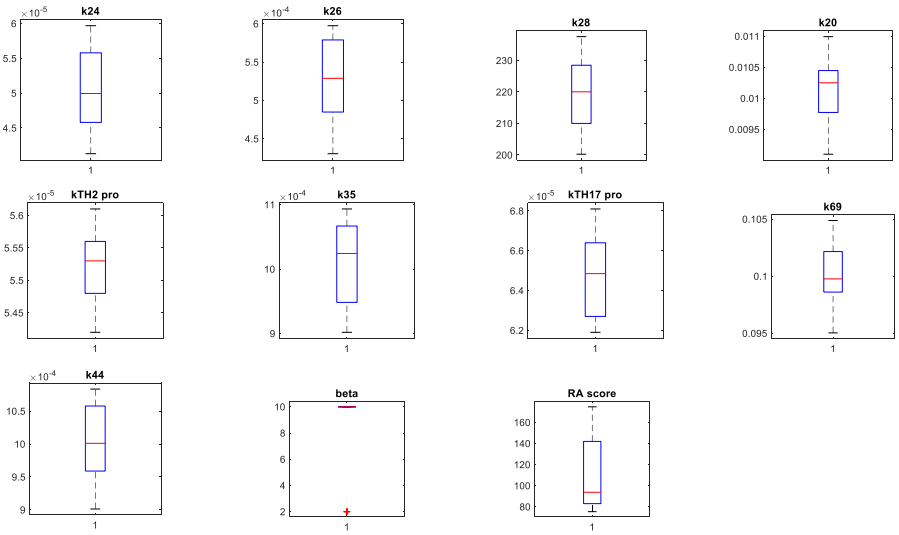


Figure 20: Estimating parameter range from clinical biomarker

CONCLUSION

In this project, the mathematical model of rheumatoid arthritis is developed and benchmarked with literature data. A study of the pharmacokinetics of the drugs abatacept, tocilizumab, and infliximab is performed, and also the corresponding pharmacodynamics is studied. A population study also reveals the percentage of the population prone to disease in the healthy condition and the population in the diseased state but healthy. A population analysis for the drug's effect shows the movement of the population towards a healthy state.

FUTURE DIRECTION

Only a preliminary step in relating the SNPs is done as a part of genomic study. A detailed genomic analysis can be done for rheumatoid arthritis to get a better understanding about the disease.

A clinical study can be done and the current model can be tested to know its performance.

This model can be applied to the newly invented drug to test its efficiency.

APPENDIX I

Table 11: Parameters used in the model

Notation	Description	Value
$beta$	Function of Citrullination	0 – Healthy, > 0 Diseased
k_{n1}	Basal APC activation in the synovium	0.1
k	The coefficient for APC activation in the synovium	0.01
k_s	APC source in synovium	2
k_d	APC degradation in the synovium	0.01
k_{36}	Activated APC degradation synovium	0.01
k_{35}	The proliferation of activated APC by Autoantibodies in the synovium	0.001
k'_{35}	Michalis Menton constant for the proliferation of activated APC by Autoantibodies in the synovium	20
k_{44}	The proliferation of activated APC by TNFα in the synovium	0.001
k'_{44}	Michalis Menton constant for the proliferation of activated APC by TNFα in the synovium	10
k_{23}	The proliferation of activated APC by IL17 in the synovium	0.001
k'_{23}	Michalis Menton constant for the proliferation of activated APC by IL17 in the synovium	5
k_{20}	Activated APC translocation from synovium to lymph node	0.01
k_{s2}	Source of T-cells in the synovium	10
k_{d2}	Degradation of T-cells in the synovium	0.01
k_{54}	Basal Th17 production in synovium from T-cells	0.0001

k_3	Basal Treg production in synovium from T-cells	0.01
k_{48}	Inhibition of Treg production by IL6 in the synovium	200
k_{52}	Inhibition of Treg production by TNFα in the synovium	10
k_{t1}	Translocation of T-cells from lymph node to synovium	0.001
k_{47}	Degradation of Th17 in the synovium	0.0097
k_{46}	Th17 proliferation by IL6 and activated APC in the synovium	0.000005
k'_{46}	Michalis Menton constant for Th17 proliferation by IL6 and activated APC in the synovium	100
k_{t4}	Translocation of Th17 from lymph node to synovium	0.0012
k_{n6}	The proliferation of Treg by TGFβ in the synovium	1
k'_3	Michalis Menton constant for the proliferation of Treg by TGFβ in the synovium	50
k_{13}	Degradation of Treg in the synovium	0.01
k_{t2}	Translocation of Treg from lymph node to synovium	0.0001
k_4	TGFβ production from Treg in the synovium	0.0002
k_{10}	Degradation of TGFβ in the synovium	0.1
k_{50}	IL6 production by activated APC in the synovium	0.1
k_{66}	IL6 production by FLS in the synovium	0.3
k_{49}	Degradation of IL6	0.15
k_{55}	Production of IL17 in the synovium	0.01
k_{n2}	Source of IL17 in synovium	0.1
k_{n3}	Production of IL17 from Th17 in the synovium	10
k'_{55}	Michalis Menton constant for production of IL17 from Th17 in the synovium	50

k_{56}	Degradation of IL17 in the synovium	0.008
k_{64}	TNFα production from Th17 in the synovium	15
k_{74}	TNFα production from activated APC in the synovium	15
k_{45}	Degradation of TNFα in the synovium	217
k_{t3}	Translocation of Autoantibodies from lymph node to synovium	0.1
k_{38}	Degradation of Autoantibodies	0.1
k_{s3}	Source of Osteoclast	1
k_5	Osteoclast proliferation by TGFβ in the synovium	0.0001
k'_5	Michalis Menton constant for Osteoclast proliferation by TGFβ in the synovium	2
k_8	Osteoclast proliferation by RANKL in the synovium	0.01
k'_8	Michalis Menton constant for Osteoclast proliferation by RANKL in the synovium	150
k_{57}	Osteoclast proliferation by IL17 in the synovium	0.2
k'_{57}	Michalis Menton constant for Osteoclast proliferation by IL17 in the synovium	200
k_{71}	Osteoclast proliferation by Autoantibodies in the synovium	0.1
k'_{71}	Michalis Menton constant for Osteoclast proliferation by Autoantibodies in the synovium	120
k_{62}	Degradation of Osteoclast	0.1
k_{s4}	Source of FLS	0.1
k_9	FLS proliferation by TGFβ in the synovium	0.0001
k'_9	Michalis Menton constant for FLS proliferation by TGFβ in the synovium	1
k_{58}	FLS proliferation by IL17 in the synovium	0.1
k'_{58}	Michalis Menton constant for FLS proliferation by IL17 in the synovium	5
k_{61}	Degradation of FLS	0.01

k_7	Production of RANKL by FLS	0.1
k_{n4}	Production of RANKL by FLS	1
k_7'	Michalis Menton constant for the production of RANKL by Th17 in the synovium	20
k_{73}	RANKL production by T-cells in the synovium	0.0001
k_{11}	Degradation of RANKL in the synovium	0.1
k_{22}	Degradation of activated APC in the lymph node	0.01
k_{sTcell}	Source of Tcell in the lymph node	10
k_{dTcell}	Degradation of Tcell in the lymph node	0.01
k_1	Basal Treg production in the lymph node from T-cells	0.01
k_{34}	Inhibition of Treg production by IL6 in the lymph node	100
k_{29}	Inhibition of Treg production by TNFα in the lymph node	100
k_{24}	Basal Th2 production in the lymph node from T-cells	0.00005
k_{26}	Basal Th17 production in the lymph node from T-cells	0.0005
k_p	Treg proliferation by TGFβ in the lymph node	0.01
k'_1	Michalis Menton constant for Treg proliferation by TGFβ in the lymph node	10
k_{16}	Degradation of Treg in the lymph node	0.01
k_{th2pro}	Th2 proliferation by IL4 in the lymph node	0.000055
k'_{24}	Michalis Menton constant for Th2 proliferation by IL4 in the lymph node	3
k_{25}	Degradation of Th2 in the lymph node	0.0085
$k_{th17pro}$	Th17 proliferation by IL4 in the lymph node	0.000065
k'_{26}	Michalis Menton constant for Th17 proliferation by IL6 in the lymph node	5
k_{27}	Degradation of Th17 in the lymph node	0.01
k_{s5}	Basal production of TNFα in the lymph node	10
k_{28}	Production of TNFα by Th17 in the lymph	217

	node	
k_{30}	Degradation of TNFα in the lymph node	217
k_{31}	Autoantibody production by Th2 in the presence of IL4 and IL6 in the lymph node	10
k'_{31}	Michalis Menton constant for Autoantibody production by Th2 in the presence of IL4 in the lymph node	30
k''_{31}	Michalis Menton constant for Autoantibody production by Th2 in the presence of IL6 in the lymph node	6
k_{33}	Inhibition of Autoantibody production by TGFβ in the lymph node	100
k_{32}	Degradation of Autoantibody in the lymph node	0.01
k_2	Production of TGFβ by Treg in the lymph node	0.01
k_{14}	Degradation of TGFβ in the lymph node	1
k_{67}	Production of IL4 in the lymph node	1
k_{s6}	Basal source of IL4 in the lymph node	0.1
k_{n5}	Production of IL4 by Th2 in the lymph node	10
k'_{67}	Michalis Menton constant for production of IL4 by Th2 in the lymph node	100
k_{68}	Degradation of IL4 in the lymph node	0.01
k_{69}	Production of IL6 by Th2 in the lymph node	0.1
k_{70}	Degradation of IL6 in the lymph node	0.1

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