Mathematical modeling and analysis using MATLAB and SimBiology to support drug development

Fulden Buyukozturk[1,*], Christina Friedrich[2]
[1]MathWorks, Inc., Natick, MA; [2] Rosa & Co LLC, San Carlos, CA; *Presenter

Introduction

Increased adaption of Quantitative Systems Pharmacology approaches in drug development [1]

Improve understanding of biology

Early and thorough *in silico* testing of drug candidates

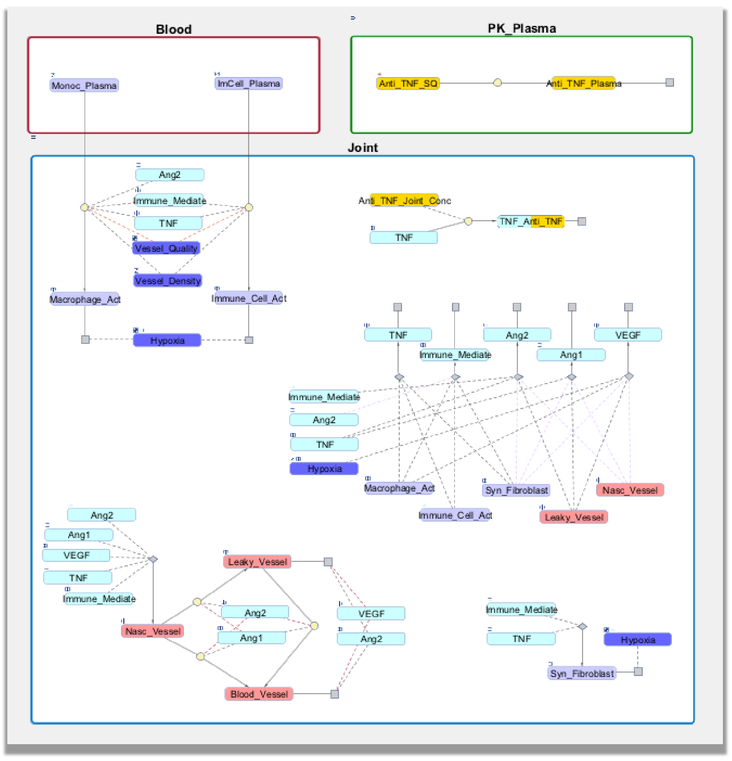
Reduce development cost and time

- Increased adoption necessitates flexible and extensible computational tools.
- **We present SimBiology, a MATLAB toolbox, as a flexible and extensible tool to streamline systems modeling and analysis in drug discovery and development.**
- **Objective:** Demonstrate the utility of SimBiology in exploring a combination therapy approach to improve clinical response to Rheumatoid Arthritis (RA) therapy.

Communicating complex disease physiology models

- Graphical representation of complex models helps with the collaboration among modelers and between modelers and non-modelers.
- **Drag and drop model diagram** in SimBiology facilitates rapid development and effective communication of models.
- **Both programmatic and graphical ways of model building.**

SimBiology implementation of a dynamic model of Rheumatoid Arthritis treatment [2]

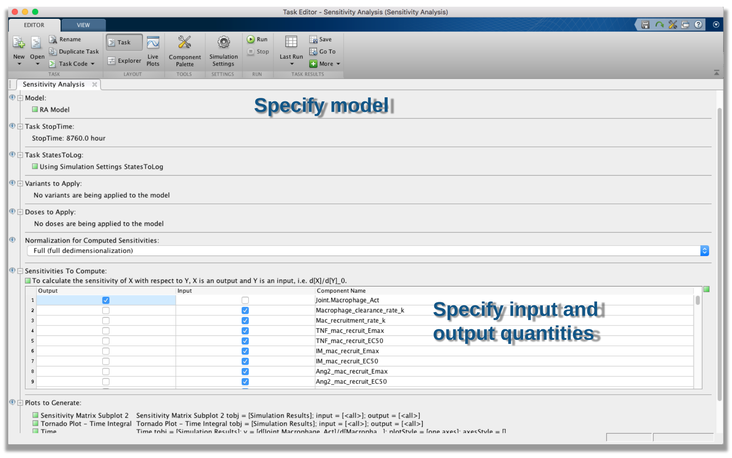


Sensitivity analysis to identify key pathways

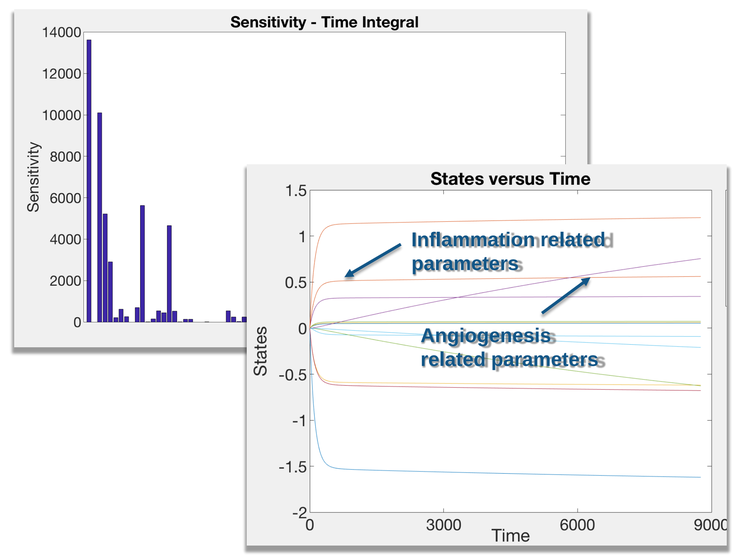
SimBiology includes functions and apps to perform common tasks in systems modeling

- **Both programmatic and interactive analysis tools**
- **Simulation** to predict system behavior
- **Sensitivity analysis** to identify significant biological pathways
- **Parameter estimation** to fit models to data

Running a sensitivity analysis task



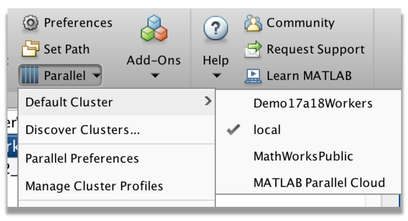
Built-in analysis results plots



- Results indicate differences in time scales
- Early driver: inflammation; late driver: angiogenesis

Parallel simulations for improved performance

- You can perform large-scale computations using multicore desktops, clusters, grids, and clouds.



In silico experiments: the effect of differences in physiology on therapy

- You can use MATLAB scripts to automate simulations and create custom analyses.
- Simulate Virtual Patients (VPs) to investigate different hypotheses about the model.

Running SimBiology models from a MATLAB script

```
%% Load Model
sbioloadproject('RAModel', 'm1') ;

%% Select anti-TNF Dosing
dose = sbioselect(m1, 'Name', 'antiTNF_50mg_Q4W') ;

%% Select variants
% Get model's variant storing Virtual Patient representations
variants = sbioselect(m1, 'Name', {'VP0','VP1','VP2'});
nVariants  = length(variants);

%% Simulation Setup
% Get configuration settings
cs = getconfigset(m1)  ;
% Set sampling times
tObs          = 0:20:8760; % hours
nTPoints      = numel(tObs);
cs.SolverOptions.OutputTimes = tObs  ;
% Create simfunction
sf = createSimFunction(m1, pNamesAll, {'Macrophage_Act','Leaky_Vessel'}, dose, 'UseParallel', true) ;
%% Simulate for each Virtual Patient
speciesNames = {'Macrophage_Act','Leaky_Vessel'};
nSpecies = length(speciesNames);
% Get dose table
dExp = getTable(dose);
% Simulate without any treatment
sd1 = sf(variants, [], [], tObs);
ResponseNoTreatment = [sd1.Data];
% Simulate with anti-TNF treatment
sd2 = sf(variants, [], dExp, tObs);
ResponseTNF = [sd2.Data];
```

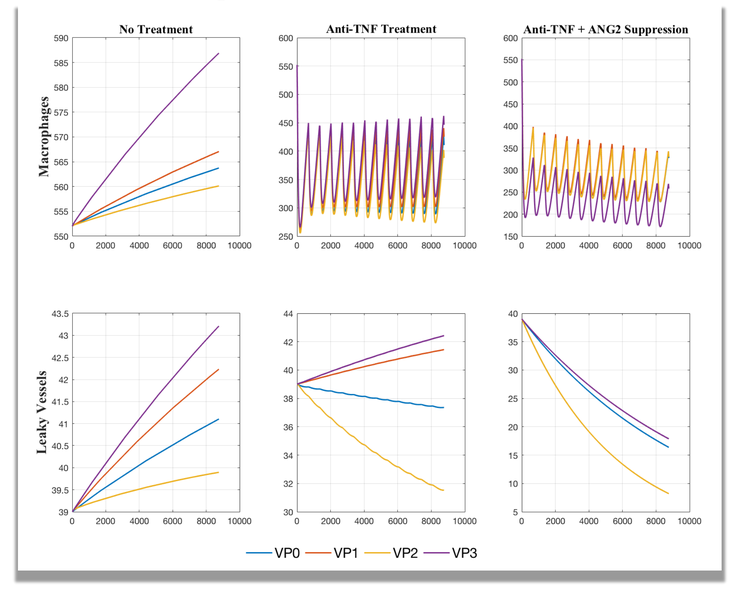
Load model

Choose different model parameterizations (VPs)

Create a function to execute the model

Simulate the model scanning across VPs

Results showing simulations for different VPs



- The combination treatment improves patient outcomes.
- VP3 benefits more than others.

References

1. Gadkar, K., Kirouac, D.C., Mager, D.E., van der Graaf, P.H., Ramanujan, S., *A Six-Stage Workflow for Robust Application of Systems Pharmacology, CPT Pharmacometrics Systems Pharmacology*, 5, 235, 2016.
2. Rheumatoid Arthritis (RA) PhysioPD™ Platform developed by Rosa & Co LLC.

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