Introduction:

I chose to look at the tumor growth models, as I believe that with the recent advances in technology, such as the use of NGS techniques and data, as well as advances in the understanding of other related processes such as angiogenesis, resistance and immunology, tumor growth can be modeled to more accurately predict the increase or decrease in the tumor burden as a result of drug intervention.

Increased knowledge of the inter-tumor and intratumor environment can help with personalized treatment and help understand treatment failure via modeling and simulation, using quantitative characterization to predict relationships between 'drug exposure/pharmacokinetics (PK), drug effects/pharmacodynamics (PD), and disease progression' [1]. The goal is to lead to a more successful treatment process and hence support drug decision making.

Looking at solid tumors particularly, the tumor size (in terms of tumor diameter and volume) are an important datapoint, especially for measuring anticancer drug effectiveness. The specific type of data collected depend on the particular modeling strategy being looked at, such as agent-based model, image-based models, multiscale model, PK/PD models, and using, more recently, tumor gene sequencing techniques [1]. Other factors that are important to look at include the genetic mechanisms such as mutations as well as genetic regulation, epigenetic mechanisms such as epigenetic modifications which can change gene expression patterns as well as posttranslational, pharmacokinetic and microenvironment mechanisms [2]

The researchers in the paper by Yin A., Moes D., et al, 2019 also conducted their review based on several factors. The mode of tumor growth was looked at, and the different growth patterns were observed (such as linear vs exponential or a combination of both), with logistic (assuming growth is limited by carrying capacity) and Gompertz (assumes growth rate decreases over time) growth models providing a more realistic change in growth rate as the tumor burden increases [1].

The next factor considered was tumor heterogeneity, using ODEs to determine tumor burden based on the different types of cells, such as whether the tumor is made up of proliferative or quiescent cells, as well as whether the tumor cells are drug-sensitive or drug-resistant. Here the concept of acquired resistance is also important, as they are assumed to increase exponentially from damaged sensitive cells after treatment. Similarly, another categorization is of androgen-dependent and androgen-independent cells.

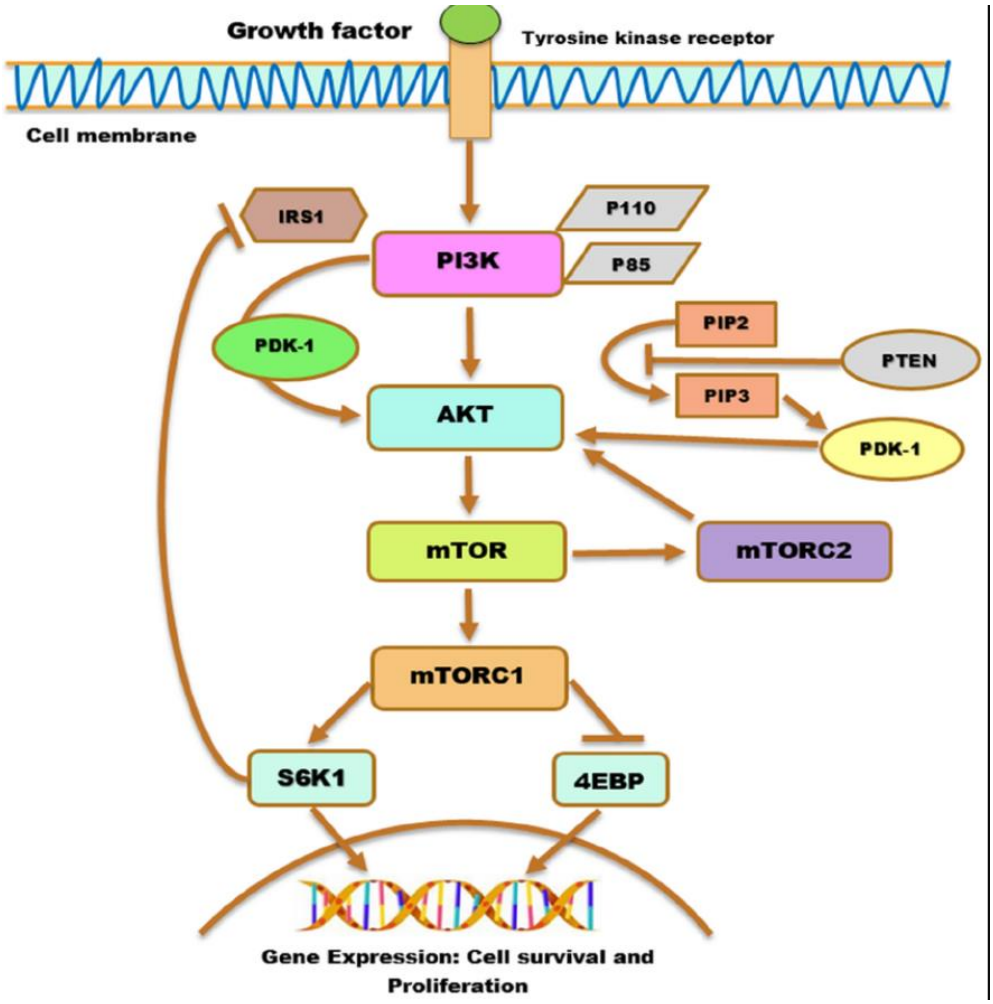
Other microenvironment factors can also be considered, such as angiogenesis (e.g. the concentration of vascular endothelial growth factor (VEGF), which helps with prediction of tumor progression) as well as the immune system interactions, such as the effect of the amount of cytotoxic T lymphocytes on the tumor cell decline rate [1].

Another factor that was looked at was the treatment effect on the tumor burden, such as the time curves for tumor shrinkage as a result of drug treatment using ODE dynamic models [1]. The paper divides the types of models into three broad categories: the tumor growth models, the treatment affect models, and the tumor resistance evolution models. These are then further differentiated based on probability, stochastic or ODE models. The choice of the type of model to look at depends on the research questions being studied. I have summarized these factors in figure 1.

I looked at the mammalian target of rapamycin (mTOR) signaling pathway as an example for the biological systems pathway for tumor growth. According to the paper by Zou Z., Li H. & Zhu X., 2020, mTOR regulates cell proliferation, autophagy and apoptosis through various signaling pathways. These pathways have also been implicated in cancer, in addition to other diseases, by over activating cell proliferation and immune cell differentiation (via gene and protein synthesis regulation) as well as tumor metabolism.

In tumor cells, the abnormally activated mTOR sends signals for tumor cells to grow, metastasize, and invade healthy tissues [3]. The most notable mutation is the PI3K/phosphate and fungi homology deletion on chromosome 10 (PTEN)/AKT/TSC pathway for the mTORC1, leading to malignant tumors. Often the PTEN expression is eliminated by 'epigenetic, genetic, and post-transcriptional modification' and the PI3K/Akt/mTOR pathway is upregulated, as shown in figure 1.

Figure 1: PI3K/Akt/mTOR pathway (Sharma et al, Medical Oncology, 2022)



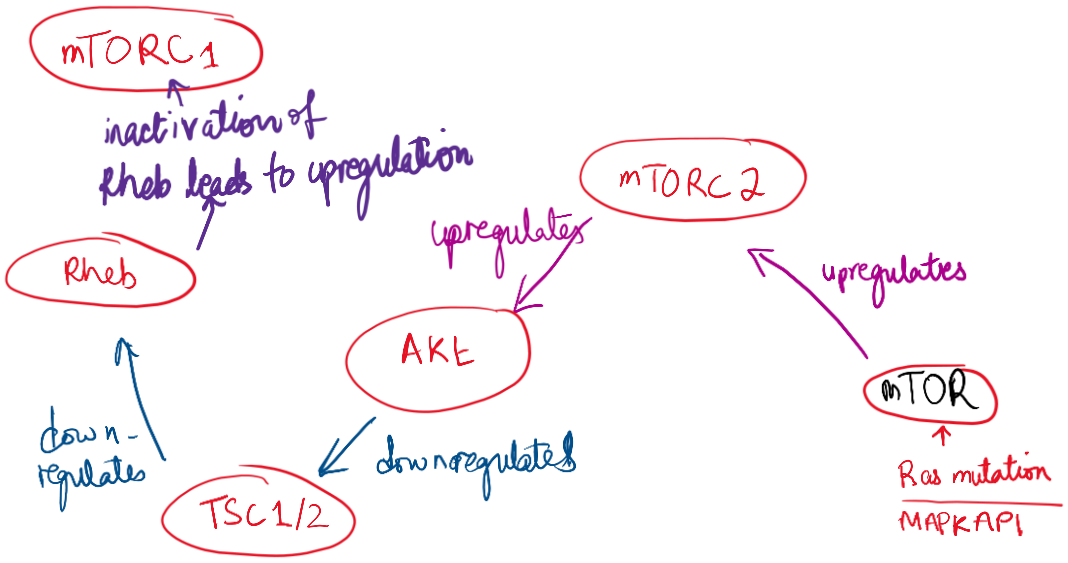


Figure2: mTOC1 upregulation via mTORC2/Akt/TSC/Rehb pathway

Another pathway which also leads to mTORC1 upregulation is via the mTORC2/Akt/TSC/Rehb pathway. The GTPase Ras mutation, which leads to the abnormal constant activation of Ras, results in the abnormal activation of the mTORC2 (either through the PI3K-dependent pathway or independent pathways). The Activated mTORC2 leads to the phosphorylation and activation of AKT, which in turn inhibits TSC1/2 complex. This down-regulates its ability to act as a GTPase-activating protein (GAP) towards Rheb. As the TSC1/2 complex usually converts the active form Rheb-GTP to its inactive form Rheb-GDP, the inhibition of TSC leads to the active Rheb activating mTORC1, which increases protein synthesis, cell growth and proliferation abnormally, leading to many forms of cancer, as shown in Fig 2.

There are several variables involved in this pathway:

- R: Ras
- M2: mTORC2
- A: AKT
- T: TSC
- Rh: Rheb
- M1: mTORC1

For any linear system, we need to develop certain assumptions for the parameters to hold true. I will make the following assumptions:

- Ras is continually activated (due to its mutated form)
- M2 is directly influenced by Ras (assuming a proportional increase)
- A activation is proportional to M2 activity
- T inhibition is inversely proportional to AKT activity (A)

- Rh is also inversely affected by T (since TSC inhibits Rheb)
- M1 is directly proportional to Rh.

The system of linear equations would then be as follows:

1. M2 activation: $dM2/dt = k_1R - d_1M2$

k_1 is the constant rate of activation by Ras and d_1 is the degradation rate of M2

2. A activation: $dA/dt = k_2M2 - d_2A$

k_2 is the rate constant by M2 activation and d_2 is the degradation rate of AKT

3. T inhibition: $dT/dt = -k_3A + d_3T$

$-k_3$ is the rate constant for inhibition by AKT and d_3 is the recovery rate of TSC

4. Rh activation: $dRh/dt = -k_4T + d_4Rh$

$-k_4$ is the rate constant for inhibition by TSC and d_4 is the rate of increase of Rheb activity

5. M1 activation: $dM1/dt = k_5Rh - d_5M1$

k_5 is the rate constant for activation by active Rheb and d_5 is the degradation rate of M1.

Based on the readings [4], I then created a state space representation which would include a state vector (representing my variables), a system dynamics matrix representing the constants, as well as the input matrix (which is also a constant). The matrix representation of the system would be:

$$dx/dt = Ax + b$$

Method and Results:

For the final model, I used the PI3K/AKT/mTOR pathway, which is a signaling pathway important in regulating cellular processes such as cell growth, proliferation, survival, and metabolism. Very briefly, PI3K activates PIP2 to PIP3, which serves as the docking site for AKT, recruiting it to the cell membrane. Once activated, AKT activates the mTOR complex, which is important for protein synthesis and cell growth [5]. I made this adjustment to the model based on the Delle Pezze paper, 2012, from where I will be using the parameters for these variable equations.

In order to create the model, after some research for papers studying the pathway, I used the sinks and sources concept mentioned in the readings to develop the ODE equations for the species, shown below. I used the parameters identified in the Dalle Pezze et al, 2012 study and created a simplified ODE version of the PI3K/AKT/mTOR pathway in MATLAB, as shown in Fig 3 below:

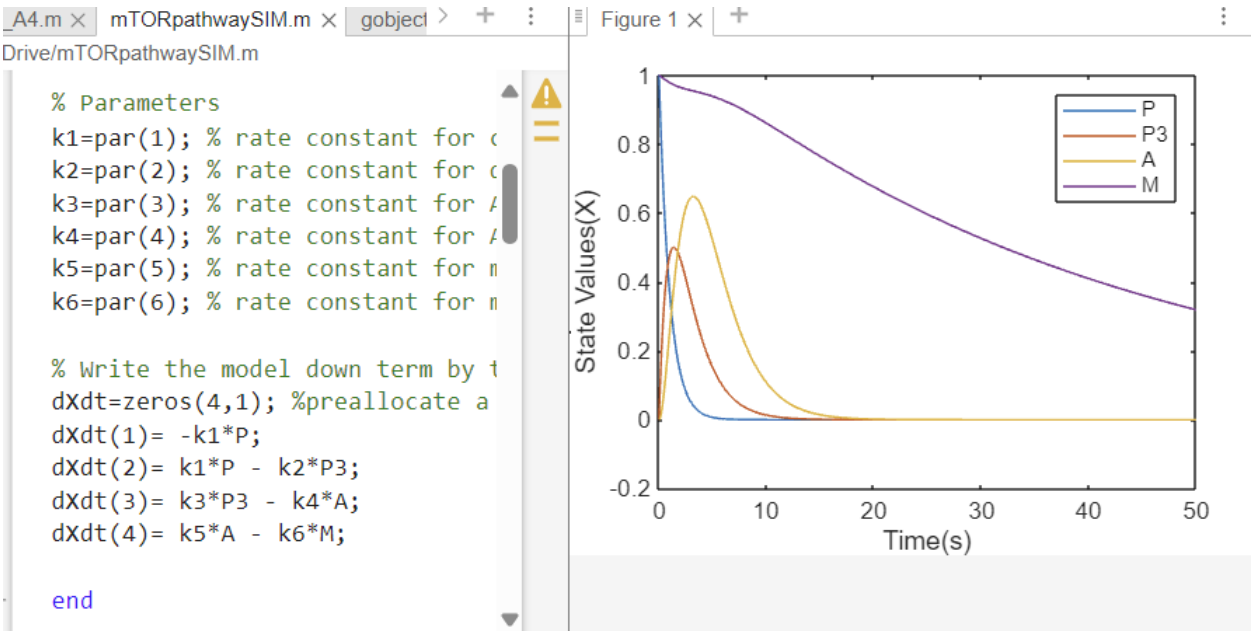


Figure 3: PKPD Model for the mTOR pathway using MATLAB

The parameters I used were also identified from the associated files from the Delle Pezze model, 2012, shown below:

```
par(1)=1; rate constant for conversion of PIP2 to PIP3 by PI3K
par(2)=0.5; rate constant for degradation of PIP3
par(3)=1; rate constant for Akt activation
par(4)=.5; rate constant for Akt deactivation
par(5)=0.025; rate constant for mTOR activation
par(6)=0.025; rate constant for mTOR deactivation
```

Although the original figure identified in the research study (Fig 4) had additional variables as well, the overall distribution of the relevant variables seems somewhat similar, especially for the final mTOR species, which both seem to decrease over time:

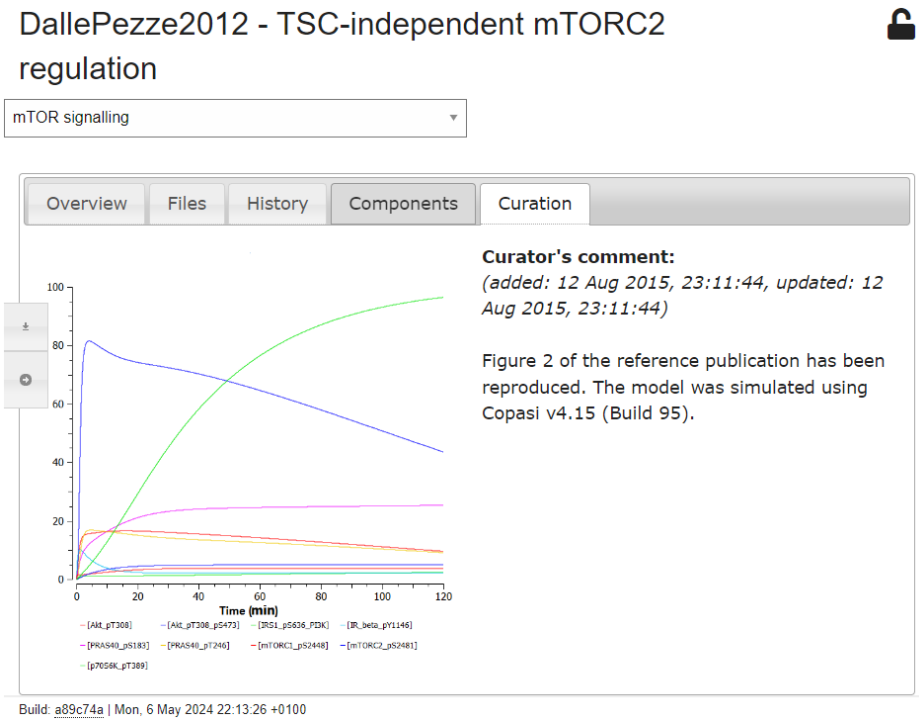


Figure 4: Figure Provided by Dalle Pezze, 2012 - TSC-inf mTORC2

In order to determine if the model needed any modifications based on the reading for the alternative models that can be applied to biological systems that may either be non-linear, or may have different mechanisms that can be better understood via these other models, I looked at the type of relationship between the species involved. As part of the research, I looked at some more research papers related to the PI3K/AKT/mTOR pathway model, and it seems that they all mainly utilize ODEs for developing their models. Looking at the online BioPortal database, I studied the relation between the key species within the pathway, and it seems that the relationship is fairly linear, as shown in the example below [8]:

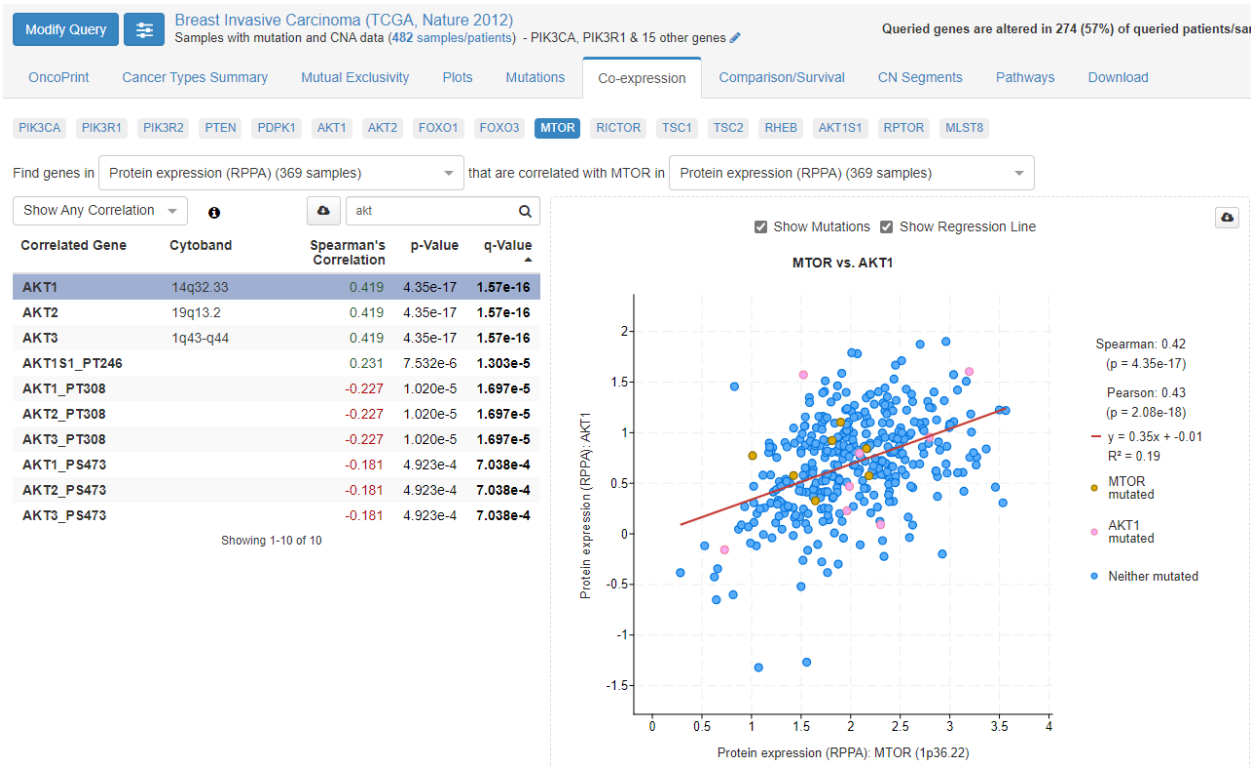


Figure 5: linear relationship between AKT and mTOR

The figure 5 shows the linear regression line for the relationship between protein expression for AKT and mTOR in the breast invasive Carcinoma (TCGA, Nature 2012) samples. The same is also true for the relation between PI3K and mTOR as shown in Fig 6.

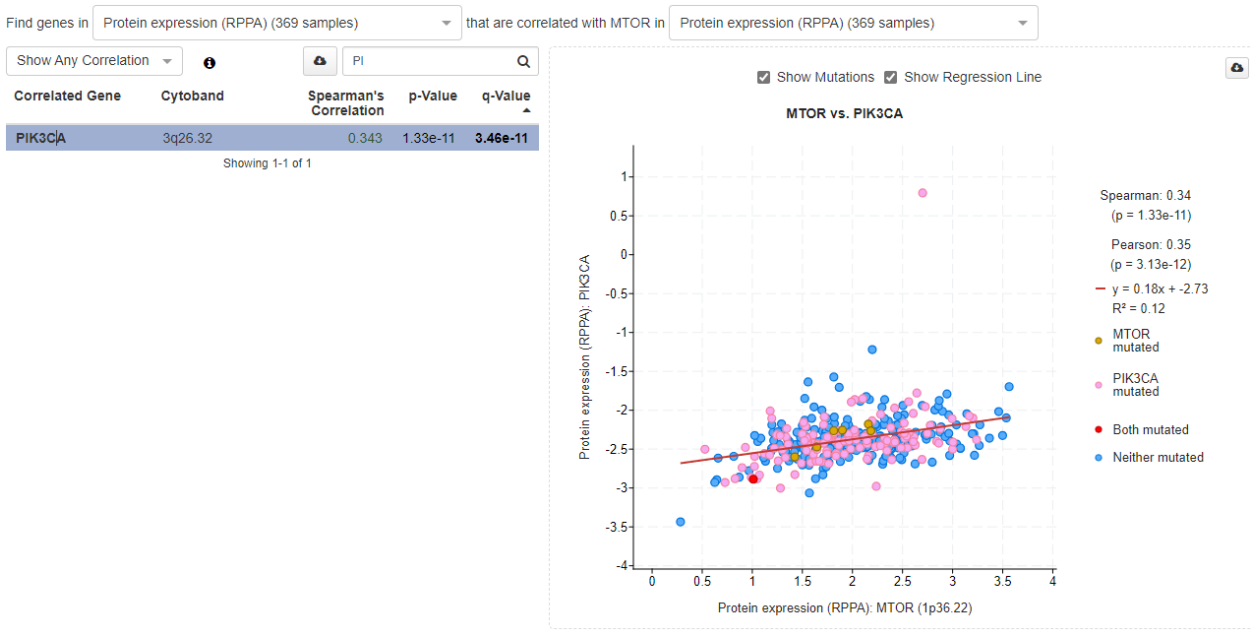


Figure 6: Linear relationship between mTOR and PIK3CA

Since the PI3K/AKT/mTOR pathway model is a fairly straightforward linear model which is adequately defined by the ODEs, I decided to keep the model as it is.

I also carried out a sensitivity analysis for the model. Based on the results from the sensitivity analysis (provided in the MATLAB code), the last parameter is the most sensitive, as small perturbations lead to much larger changes in its values, especially when compared with the other parameters. This suggests that changes in that parameter would lead to a significant impact on the dynamics of the pathway. Since mTOR is an important species being the end target of the pathway, understanding how this parameter affects the entire system is crucial for accuracy of the model. This is important if we hope to use this pathway effectively for disease intervention, especially for targeted cancer treatments. Since it seemed to follow the same trajectory as in the BioModels graph, I decided to leave the parameter as is for my model.

****Adding the MATLAB code here ****

```
%% ODE for mTORC1 upregulation via PI3K/AKT/mTOR pathway
clear all;
close all;
% defining the function for the mTORC1 upregulation
function dXdt=modelODE(t,X,par)

% State vectors
P=X(1);
P3=X(2);
A=X(3);
M=X(4);

% Parameters
k1=par(1); % rate constant for conversion of PIP2 to PIP3 by PI3K
k2=par(2); % rate constant for degradation of PIP3
k3=par(3); % rate constant for Akt activation
k4=par(4); % rate constant for Akt deactivation
k5=par(5); % rate constant for mTOR activation
k6=par(6); % rate constant for mTOR deactivation

% Write the model down term by term
dXdt=zeros(4,1); % preallocate a column vector
dXdt(1)= -k1*P;
dXdt(2)= k1*P - k2*P3;
dXdt(3)= k3*P3 - k4*A;
dXdt(4)= k5*A - k6*M;

end

% Run model
% clear all variables from workspace
% clear all

% close all open figures from workspace
```

```
% close all

% Define the Initial Conditions of the system
IC=[1;0;0;1];

% Set the parameter values for the parameters ‘p’ vector
par(1)=1;
par(2)=0.5;
par(3)=1;
par(4)=.5;
par(5)=0.025;
par(6)=0.025;

% DESCRIPTION:
% anonymize the function call, and assign the parameter set to this
% anonymized function

% Create an anonymous function ‘f’ that represents the system of ODEs
% INPUTS: The function ‘f’ takes two arguments, ‘t’ (time) and ‘x’ (state vector)
% OUTPUTS: The function returns the output ‘MyModel(t,x,p)’
f=@(t,X)modelODE(t,X,par);

% Define the timespan over which the ODEs will be solved
T=[0 50];

% set default options for ODE solver
options=odeset;
% specify absolute and relative tolerances for ODE solver to control for solution
% accuracy
options.AbsTol=1e-6;
options.RelTol=1e-6;

% The code below solves the system of ODEs using the ‘ode15’ solver
% INPUTS:
% F: function handle
% T: time vector
% IC: initial conditions vector
% options: solver options

% Outputs:
% T: time vector with time points at which the solution was computed
% X: solution matrix, with each row corresponding to the state values of the
% system at the corresponding time in ‘T’
[TSol,XSol]=ode45(f,T,IC,options);
plot(TSol,XSol(:, 1))
hold on
plot(TSol,XSol(:,2))
hold on
plot(TSol,XSol(:,3))
hold on
plot(TSol,XSol(:,4))
xlabel("Time(s)");
ylabel("State Values(X)");
legend("P","P3", "A", "M");
hold off
```

```
%% Sensitivity Analysis

% Preallocate sensitivity vector
sensitivity = zeros(length(TSol), length(par));
for i = 1:length(par)
% Perturb parameter
perturbed_pars = par;
perturbed_pars(i) = 1.1 * par(i); % perturb parameter by 10%
% Solve the ODE with perturbed parameters
[TSen, x_perturbed] = ode45(@(t, X) modelODE(t, X, perturbed_pars), T, IC, options);
% Ensure x_perturbed is interpolated to match the same time points as TSol
x_perturbed_interpolated = interp1(TSen, x_perturbed, TSol, 'linear', 'extrap');
% Calculate sensitivity at each time point
sensitivity(:, i) = (x_perturbed_interpolated(:, end) - XSol(:, end)) / (0.1 *
par(i));
end

% Display local sensitivities

disp('Local Sensitivities: ');
disp(sensitivity);
```

Citations:

[1] Yin A., Moes D., et al, 2019, A Review of Mathematical Models for Tumor Dynamics and Treatment Resistance Evolution of Solid Tumors, CPT Pharmacometrics Syst Pharmacol, A Review of Mathematical Models for Tumor Dynamics and Treatment Resistance Evolution of Solid Tumors - PMC (nih.gov)

[2] Sun X., Hu B., 2018, Mathematical modeling and computational prediction of cancer drug resistance, Brief Bioinform, Mathematical modeling and computational prediction of cancer drug resistance - PMC (nih.gov)

[3] Zou, Z., Tao, T., Li, H. *et al.* mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges. *Cell Biosci* **10**, 31 (2020). https://doi.org/10.1186/s13578-020-00396-1

[4] Sharma et al, Myricetin-induced apoptosis in triple-negative breast cancer cells through inhibition of the PI3K/Akt/mTOR pathway, Medical Oncology, 39, 2022, 10.1007/s12032-022-01856-z

[5] Interactions among mTORC, AMPK and SIRT: a computational model for cell energy balance and metabolism - PMC (nih.gov)

[6] Frontiers | Computational Modeling of the Metabolic States Regulated by the Kinase Akt (frontiersin.org)

[7] Dalle Pezze P, Sonntag AG, Thien A, Prentzell MT, Gödel M, Fischer S, Neumann-Haefelin E, Huber TB, Baumeister R, Shanley DP, Thedieck K., Sci Signal 2012 Mar; 5(217), DallePezze2012 - TSC-independent mTORC2 regulation | BioModels (ebi.ac.uk).

[8] cBioPortal for Cancer Genomics: PIK3CA, PIK3R1 and 15 other genes in Breast Invasive Carcinoma (TCGA, Nature 2012)

[9] DallePezze2012 - TSC-independent mTORC2 regulation | BioModels (ebi.ac.uk)

[10] Sonntag2012 - mTOR model - IRS dependent regulation of AMPK by insulin | BioModels (ebi.ac.uk)

[11] © Copyright 2005 to 2022 Erik Cheever, State Space Representations of Linear Physical Science, State Space Representations of Linear Physical Systems (swarthmore.edu)