# Model simulation TTP core

clear

clc

**p38 MAPK-TTP pathway**

Dependent Variables

 LPS= 1;%ng/mL

 PP = 1; % [PP2A]

Parameters

% gammai = synthesis rate of i

% deltai = degradation rate of i

% phii = phosphorylation rate of i

% rhoi = de-phosphorylation rate of i

% p38\_P (Pp)

phiPp = 0.1;

rhoPp = 0.01;

%rhoPp = 0; % Simulation DUSP KO (linear does not work)

% TTP (T),

gammaT= 1; % tbc, testing

%gammaT= 0; % Simulation TTP KO phenotype

deltaT = 0.2; % tbc, resting state

phiT = 50; % tbc, testing

%phiT = 0; % Simulation AA mutant

% TTP\_P (Tp),

deltaTp = 0.000001;

rhoTp = 0.05; %tbc,

%rhoTp = 0; % Simulation PP2A inhibitor

% Target mRNA (Rm),

gammaRm = 1; % tbc

deltaRm1 = 0.001; % tbc, resting state: gammam1=deltam1\*mRNA+deltam2\*TTP

deltaRm2 = 0.1; % tbc

Initial conditions

Pp0=0;

T0=0;

Tp0=0;

Rm0=0;

Final timepoint

tend = 480; % [min]

% filename = sprintf('TablesTTP/TTP\_simulation\_202406011.csv');

% TTP KO

% filename = sprintf('TablesTTP/TTP\_KO\_simulation\_20240612.csv');

% gammaT = 0;

% % DUSP KO

% filename = sprintf('TablesTTP/TTP\_DUSPKO\_simulation\_20240612.csv');

% rhoPp = 0;

% % AA

% filename = sprintf('TablesTTP/TTP\_AA\_simulation\_20240612.csv');

% phiT = 0;

% % PP2Ai

% filename = sprintf('TablesTTP/TTP\_PP2Ai\_simulation\_20240612.csv');

% rhoTp = 0;

ODE Solver

options = odeset('RelTol',1e-5); %

% Solve ODEs

[t,x] = ode23(@TTP\_v1,[0 tend],[Pp0 T0 Tp0 Rm0],options,LPS,PP,phiPp,rhoPp,gammaT,deltaT,phiT,deltaTp,rhoTp,gammaRm,deltaRm1,deltaRm2);

% tbc ode23 (Ffion uses differnt ode solver: ode15s)

Data generation

% define figure labels

ylabs= {'p38-P [a.u]'; 'TTP [a.u.]'; 'TTP-P [a.u.]'; 'target mRNA [a.u]'};

% define fontsize and style for consistent use below and physical figure size

% plot figure

for k=1:4 % forloop

 subplot(2,2,k), hold all %

 plot(t, x(:,k));

 xlabel('Time (min)')

 ylabel(ylabs(k))

end

dx = linspace(0,tend,tend+1);

dy = interp1(t,x,dx);

Tv1 = table(dx',dy);

writetable(Tv1,filename);

Function TTP

function f=TTP\_v1(t,x,LPS,PP,phiPp,rhoPp,gammaT,deltaT,phiT,deltaTp,rhoTp,gammaRm,deltaRm1,deltaRm2)

Pp = x(1);

T = x(2);

Tp = x(3);

Rm = x(4);

Ppdiff=phiPp\*LPS - rhoPp\*Pp\*t;

Tdiff = gammaT\*Pp - phiT\*T\*Pp - deltaT\*T + rhoTp\*Tp\*PP;

Tpdiff = phiT\*T\*Pp - deltaTp\*Tp - rhoTp\*Tp\*PP;

Rmdiff = gammaRm\*Pp - deltaRm1\*Rm - deltaRm2\*T\*Rm;

f=[Ppdiff Tdiff Tpdiff Rmdiff]';

end

# Model simulaiton Kulawik p38 MAPK

clear

clc

**P38 MAPK pathway by Kulawik & Bode 2017**

 IL=20;%ng/mL

Parameters

% gammai = synthesis rate of i

% deltai = degradation rate of i

% phii = phosphorylation rate of i

% rhoi = de-phosphorylation rate of i

ILsat=+0.524\*10^(-1);

phiMK=+1.02\*10^(+1);

rhoMKp=+7.14\*10^(-1);

deltaD=+0.01;

gammaD=+8.41\*10^(-3);

phiP1=+1.51\*10^(-4);

phiP2=+9.08\*10^(-3);

rhoPp1=+1.0\*10^(-5);

rhoPp2=+3.10\*10^(+1);

Initial conditions

P0=0.3577;%mikroM

Pp0=0.0013;

D0=0;

MK0=4.5514;

MKp0=0.0856;

Final timepoint

tend = 100; % [min]

ODE Solver

options = odeset('RelTol',1e-5); %

% Solve ODEs

[t,x] = ode23(@Kulawik\_v1,[0 tend],[P0 Pp0 D0 MK0 MKp0],options,IL,ILsat,phiMK,rhoMKp,deltaD,gammaD,phiP1,phiP2,rhoPp1,rhoPp2);

% tbc ode23 (Ffion uses differnt ode solver: ode15s! ask Sara)

Figure p38MAPK

filename = sprintf('TablesKulawik/Kulawik\_simulation\_20240607.csv');

% define figure labels

ylabs= {'p38 [microMol/L]'; 'pp38 [microMol/L] '; 'DUSP [a.u]'; 'MK2 [microMol/L]'; 'pMK2 [microMol/L]'};

% define fontsize and style for consistent use below and physical figure size

% % plot figure

% for k=1:5 % forloop

% subplot(2,3,k), hold all %

% plot(t, x(:,k));

% xlabel('Time (min)')

% ylabel(ylabs(k))

% end

% hold off

plot(t, x(:,2));

plot(t, x(:,5));

dx = linspace(0,tend,tend+1);

dy = interp1(t,x,dx);

Tv1 = table(dx',dy);

writetable(Tv1,filename);

Function MAPK\_TTP

function f=Kulawik\_v1(t,x,IL,ILsat,phiMK,rhoMKp,deltaD,gammaD,phiP1,phiP2,rhoPp1,rhoPp2)

P = x(1);

Pp = x(2);

D = x(3);

MK = x(4);

MKp = x(5);

Pdiff=-((P\*phiP1)+((IL\*P\*phiP2)/(IL\*ILsat+1)))+((rhoPp1\*Pp)+(D\*rhoPp2\*Pp));

Ppdiff=+((P\*phiP1)+((IL\*P\*phiP2)/(IL\*ILsat+1)))-((rhoPp1\*Pp)+(D\*rhoPp2\*Pp));

Ddiff=+(gammaD\*Pp)-(D\*deltaD);

MKdiff=-(MK\*phiMK\*Pp)+(rhoMKp\*MKp);

MKpdiff=+(MK\*phiMK\*Pp)-(rhoMKp\*MKp);

f=[Pdiff Ppdiff Ddiff MKdiff MKpdiff]';

end

# Model simulation Kulawik p38 MAPK-TTP

clear

clc

**P38 MAPK TTP pathway inspired by Kulawik & Bode 2017**

 LPS=10;%ng/mL

 %PP = 1; % [PP2A] Taken out for now for simplification

Parameters

% gammai = synthesis rate of i

% deltai = degradation rate of i

% phii = phosphorylation rate of i

% rhoi = de-phosphorylation rate of i

% %% Prelim parameter set 231221

% % P38 (P),

% phiP1=0.00015;

% phiP2=0.01;

% % P38\_P (Pp),

% rhoPp1=0.0001;

% rhoPp2=0.003;

% % DUSP1 (D),

% gammaD=0.03;

% deltaD=0.0001;

%

% % TTP (T),

% gammaT= 0.02;

% deltaT = 0.02;

% phiT = 0.003;

% % TTP\_P (Tp),

% deltaTp = 0.00001;

% rhoTp = 0.02;

% % Target mRNA (Rm),

% gammaRm = 0.04;

% deltaRm1 = 0.0001;

% deltaRm2 = 0.002;

% %Initial conditions prelim + BMDM

% P0=99.09829141;

% Pp0=8.291371;

% D0=0.0001;

% T0=7.833826667;

% Tp0=7.699146667;

% Rm0=1.948337333;

%% Estimated Parameter BMDM 280224

filename = 'Tables/KulawikTTP\_BMDM\_p38i\_PE\_simulation\_20240229.csv';

thetaB=[0.006908272 0.001142764 0 0.00229858 0.042270525 0.016056939 0.04 0.000000000000004 0.01 0.01 0.07 0.06 1.06E-16 0.0007];

% P38 (P),

phiP1=thetaB(1);

phiP2=thetaB(2);

% P38\_P (Pp),

rhoPp1=thetaB(3);

rhoPp2=thetaB(4);

% DUSP1 (D),

gammaD=thetaB(5);

deltaD=thetaB(6);

% TTP (T),

gammaT= thetaB(7);

deltaT = thetaB(8);

phiT = thetaB(9);

% TTP\_P (Tp),

deltaTp = thetaB(10);

rhoTp = thetaB(11);

% Target mRNA (Rm),

gammaRm = thetaB(12);

deltaRm1 = thetaB(13);

deltaRm2 = thetaB(14);

%Initial conditions prelim + BMDM

P0=99.09829141;

Pp0=8.291371;

D0=0.0001;

T0=7.833826667;

Tp0=7.699146667;

Rm0=1.948337333;

% %% Estimated paramater RAW 231221

% filename = 'Tables/KulawikTTP\_RAW\_PE\_simulation\_20240228.csv';

% thetaR=[1.50E-04 1.00E-02 1.00E-04 3.00E-03 3.00E-02 1.00E-04 2.00E-02 2.00E-02 3.00E-03 1.00E-05 2.00E-02 4.00E-02 1.00E-04 2.00E-03];

%

% % P38 (P),

% phiP1=thetaR(1);

% phiP2=thetaR(2);

% % P38\_P (Pp),

% rhoPp1=thetaR(3);

% rhoPp2=thetaR(4);

% % DUSP1 (D),

% gammaD=thetaR(5);

% deltaD=thetaR(6);

%

% % TTP (T),

% gammaT= thetaR(7);

% deltaT = thetaR(8);

% phiT = thetaR(9);

% % TTP\_P (Tp),

% deltaTp = thetaR(10);

% rhoTp = thetaR(11);

% % Target mRNA (Rm),

% gammaRm = thetaR(12);

% deltaRm1 = thetaR(13);

% deltaRm2 = thetaR(14);

%

% %Initial conditions RAW264.7 cells

% P0=77.920111;

% Pp0=5.079889;

% D0=0.0001;

% T0=0.0001;

% Tp0=0.0001;

% Rm0=1.159164333;

%Mutant/Inhibitor simulation

% %AA/MK2i

% phiT = 0;

% Tp0=0;

%%TTP KO

%gammaT= 0;

% %DUSPKO

% gammaD=0;

% D0=0;

%p38i

gammaD=0;

gammaRm=0;

gammaT=0;

phiT=0;

D0=0;

T0=0;

Tp0=0;

Rm0=0;

%DUSP1i

% rhoPp2=0;

% %PP2Ai

% rhoTp = 0;

% T0=0;

Final timepoint

tend = 480; % [min]

ODE Solver

options = odeset('RelTol',1e-5); %

% Solve ODEs

[t,x] = ode23(@RinkTTP\_v1,[0 tend],[P0 Pp0 D0 T0 Tp0 Rm0],options,LPS,deltaD,gammaD,phiP1,phiP2,rhoPp1,rhoPp2,gammaT,deltaT,phiT,deltaTp,rhoTp,gammaRm,deltaRm1,deltaRm2);

% tbc ode23 (Ffion uses differnt ode solver: ode15s! ask Sara)

Figure p38MAPK

% define figure labels

ylabs= {'p38'; 'pp38'; 'DUSP'; 'TTP'; 'TTP-P'; 'TNFa'};

% define fontsize and style for consistent use below and physical figure size

% plot figure

for k=1:6 % forloop

 subplot(3,2,k), hold all %

 plot(t, x(:,k));

 xlabel('Time (min)')

 ylabel(ylabs(k))

end

% Create vector space for export Excel

dx = linspace(0,tend,tend+1);

dy = interp1(t,x,dx);

figure

plot(t, x, '-b')

hold on

plot(dx, dy, '+r')

hold off

%Export data for Graphpad Prism

Tv1 = table(dx',dy);

writetable(Tv1,filename);

Function MAPK\_TTP

function f=RinkTTP\_v1(t,x,LPS,deltaD,gammaD,phiP1,phiP2,rhoPp1,rhoPp2,gammaT,deltaT,phiT,deltaTp,rhoTp,gammaRm,deltaRm1,deltaRm2)

P = x(1);

Pp = x(2);

D = x(3);

T = x(4);

Tp = x(5);

Rm = x(6);

Pdiff=-((P\*phiP1)+(LPS\*P\*phiP2))+((rhoPp1\*Pp)+(D\*rhoPp2\*Pp));

Ppdiff=+((P\*phiP1)+(LPS\*P\*phiP2))-((rhoPp1\*Pp)+(D\*rhoPp2\*Pp));

Ddiff=+(gammaD\*Pp)-(D\*deltaD);

Tdiff = gammaT\*Pp - phiT\*T\*Pp - deltaT\*T + rhoTp\*Tp;

Tpdiff = phiT\*T\*Pp - deltaTp\*Tp - rhoTp\*Tp;

Rmdiff = gammaRm\*Pp - deltaRm1\*Rm - deltaRm2\*T\*Rm;

f=[Pdiff Ppdiff Ddiff Tdiff Tpdiff Rmdiff]';

end

# Model simulation Tomida p38 MAPK

clear

clc

**Tomida & Saito 2015**

Parameters

S=1; %=0, the stimulatory input

k0=0.06; % [min^-1], rate constant for MAP2K activation (phiM)

k1=0.15; % [min^-1], rate constant for MAP2K deactivation (rhoMp)

k2=0.15; % [min^-1], rate constant for p38 MAPK activation (phiP)

k3=0.16; % [min^-1], maximum reaction rate for p38 MAPK inactivation

k4=0.0001; % equivalent to Michaelis-Menten constant for the reaction of MKP-1 mediated p38 inactivation (km)

k5=0.055; % [min^-1], rate constant MKP-1 gene transcript (gammaDm)

k6=0.05; % [min^-1], rate constant for degradation of MKP-1 gene transcript (deltaDm)

k7=0.2; % [min^-1], rate constant for MKP-1 protein expression (gammaD)

k8=0.02; % [min^-1], rate constant for MKP-1 protein degradation (deltaD)

k9=0.2; % [min^-1], rate constant for FRET reporter activation by active p38 MAPK

k10=0.05; % [min^-1], rate constant for FRET reporter inactivation

k11=0.0002; % [min^-1], rate constant for MKP-1 protein expression in the presence of tripolide

k12=0.003; % [min^-1], rate constant for MKP-1 gene transcription induced by dexamethasone treatment

Initial conditions

MAP2K0=0;

MAPK0=0;

MKP1RNA0=0;

MKP10=0;

FRET0=0;

Final timepoint

tend = 400; % [min]

ODE Solver

options = odeset('MaxStep',0.4);

[t,x] = ode23(@Tomida,[0 tend],[MAP2K0 MAPK0 MKP1RNA0 MKP10 FRET0], options,S,k0,k1,k2,k3,k4,k5,k6,k7,k8,k9,k10,k11,k12);

% k8=0.004+(0.036-0.004)\*rand(30,1) % 30 randomized values for k8

% ylabs= {'MAP2K activity a.u';'p38 activity a.u';'MKP-1 mRNA levels a.u';'MKP-1 activity a.u';'FRET'};

% for i=1:30

% [t,x] = ode23(@Tomida,[0 tend],[MAP2K0 MAPK0 MKP1RNA0 MKP10 FRET0],options,S,k0,k1,k2,k3,k4,k5,k6,k7,k8(i),k9,k10,k11,k12);

%

% dx = linspace(0,tend,tend+1);

% dy = interp1(t,x,dx);

% filename = sprintf('TablesTomida/Tomida\_simulation\_20240304\_%d.csv', i);

% Tv1 = table(dx',dy);

% writetable(Tv1,filename);

%

% for k=1:4 % forloop

% subplot(2,2,k), hold all %

% plot(t, x(:,k));

% xlabel('Time (min)')

% ylabel(ylabs(k))

%

% end

% end

Figure TTPpathway

ylabs= {'MAP2K activity a.u';'p38 activity a.u';'MKP-1 mRNA levels a.u';'MKP-1 activity a.u';'FRET'};

% plot figure

for k=1:4 % forloop

 subplot(2,2,k), hold all %

 plot(t, x(:,k));

 xlabel('Time (min)')

 ylabel(ylabs(k))

end

hold off

dx = linspace(0,tend,tend+1);

dy = interp1(t,x,dx);

filename = ('TablesTomida/Tomida\_simulation\_20240304.csv');

Tv1 = table(dx',dy);

writetable(Tv1,filename);

Function Tomida

function f=Tomida(t,x,S,k0,k1,k2,k3,k4,k5,k6,k7,k8,k9,k10,k11,k12)

MAP2K = x(1);

MAPK = x(2);

MKP1RNA = x(3);

MKP1 = x(4);

FRET = x(5);

% (i) Activation of MAP2Ks that activate p38.

MAP2Kdiff=k0\*S\*(1-MAP2K)-k1\*MAP2K;

% (ii) Activation and inactivation of p38 MAPK

MAPKdiff=k2\*MAP2K\*(1-MAPK)-k3\*MKP1\*MAPK/(k4+MAPK);

% (iii) Transcription of the MKP-1 mRNA

MKP1RNAdiff=k5\*MAPK\*(1-MKP1RNA)-k6\*MKP1RNA;

% (iv) Protein expression of MKP-1

MKP1diff=k7\*MKP1RNA\*(1-MKP1)-k8\*MKP1;

% (v) Conversion of p38 activity to the p38 FRET reporter signal

FRETdiff=k9\*MAPK\*(1-FRET)-k10\*FRET;

%Following equations were used for simulating the effects of pharmacological inhibitors

% (vi) Modification of equations (iii) in the presence of dexamethasone

%MKP1RNAdiff=k5\*MAPK\*(1-MKP1RNA)-k6\*MKP1RNA+k12\*(1-MKP1RNA);

% Modification of equation (iv) in the presence of triptolide

%MKP1diff=k11\*MKP1RNA\*(1-MKP1)-k8\*MKP1

f=[MAP2Kdiff MAPKdiff MKP1RNAdiff MKP1diff FRETdiff]';

end

# Model simulation Tomida p38 MAPK-TTP

clear

clc

**Tomida & Saito 2015**

Parameters

%Explanations

% gammai := synthesis rate of i

% deltai := degradation rate of i

% phii := phosphorylation rate of i

% rhoi := de-phosphorylation rate of i

% Xp := phosphorylated variable X

% Xm := mRNA of the variable X

% Xg := green fluorescent

S = 1; % Stimulus (LPS)

% parameter Tomida p38 MAPK (reduced)

% phiP1 = 0.00717;

phiP = 0.043; % MAP2Kmax(0.2857)\*k2(0.15) % p38 (P)

% rhoPp1 = 0.00000005;%(rhoPp2 is 3.1\*10^6 times bigger than rhoPp1 according to Kulawik)

rhoPp = 0.16; %(Mp 0.15)

km = 0.0001; % Michaelis Menten constant

gammaDm = 0.055; % DUSP1/MKP1 (D)

deltaDm = 0.05;

gammaD = 0.2;

deltaD = 0.02;

% parameter TTP pathway

gammaT = 0.018; % TTP (T) max Tp=0.4

deltaT = 0.023 %0.3; %Brook t1/2 around 30 min - 0.023 (minimum if dephos so fast that all TTP\_P is dephos within a few)

phiT = 50;

rhoTp = 0.05;

deltaTp = 0.0029; %0.0000001; (%Brook t1/2 > 4h )

gammaAm = 1; % TTP target mRNA for example TNFa (A)

deltaAm1 = 0.005; % TTP independent

deltaAm2 = 10; % TTP dependent

Initial conditions

P0 = 1; %tbc

Pp0 = 0; %tbc

Dm0 = 0; %tbc

D0 = 0; %tbc

T0 = 0; % tbc

Tp0 = 0; % tbc

Tt0 = 0;

Am0 = 0; % tbc

x0 = [P0 Pp0 Dm0 D0 T0 Tp0 Tt0 Am0];

Final timepoint

tend = 480; % [min]

ODE Solver

options = odeset('MaxStep',0.4);

% [t,x] = ode23(@TTPpathway,[0 tend],x0,options,S,DO,phiP,rhoPp,km,gammaDm,deltaDm,gammaD,deltaD,gammaT,deltaT,phiT,deltaTp,rhoTp,gammaAm,deltaAm1,deltaAm2);

Multicellular Data and simulation

% deltaD=0.004+(0.036-0.004)\*rand(50,1); % 30 randomized values for k8

% ylabs= {'p38';'p38-P';'dusp1 mRNA';'DUSP1';'TTP';'TTP-P';'TTP total';'TNF mRNA'};

% for i=1:50

%

% filename = sprintf('TablesTomidaTTP/WT/TomidaTTP\_simulation\_20240305\_%d.csv', i);

% % AA/MK2i

% filename = sprintf('TablesTomidaTTP/AA/TomidaTTP\_AA\_simulation\_20240701\_%d.csv', i);

% phiT = 0;

% Tp0=0;

% % % EE (TTP = TTP phosphorylated)

% filename = sprintf('TablesTomidaTTP/EE/TomidaTTP\_EE\_simulation\_20240701\_%d.csv', i);

% phiT = 0;

% Tp0=0;

% deltaT = 0.0029; %0.0000001;

% deltaAm2 = 0;

% %TTP KO

% filename = sprintf('TablesTomidaTTP/TTPKO/TomidaTTP\_TTPKO\_simulation\_20240701\_%d.csv', i);

% gammaT= 0;

% %DUSPKO

% filename = sprintf('TablesTomidaTTP/DUSPKO/TomidaTTP\_DUSPKO\_simulation\_20240701\_%d.csv', i);

% gammaD=0;

% D0=0;

% % p38i

% filename = sprintf('TablesTomidaTTP/p38i/TomidaTTP\_p38i\_simulation\_20240701\_%d.csv', i);

% gammaAm=0;

% gammaD=0;

% gammaT=0;

% phiT=0;

% D0=0;

% Tp0=0;

% Rm0=0;

% %DUSP1i

% filename = sprintf('TablesTomidaTTP/DUSPi/TomidaTTP\_DUSPi\_simulation\_20240701\_%d.csv', i);

% rhoPp=0;

% %PP2Ai

% filename = sprintf('TablesTomidaTTP/PP2Ai/TomidaTTP\_PP2Ai\_simulation\_20240701\_%d.csv', i);

% rhoTp = 0;

% T0=0;

% % %PP2Aa (activator)

% filename = sprintf('TablesTomidaTTP/PP2Aa/TomidaTTP\_PP2Aa\_simulation\_20240701\_%d.csv', i);

% rhoTp=5; %0.05 originally

% [t,x] = ode23(@TTPpathway,[0 tend],x0,options,S,phiP,rhoPp,km,gammaDm,deltaDm,gammaD,deltaD(i),gammaT,deltaT,phiT,deltaTp,rhoTp,gammaAm,deltaAm1,deltaAm2);

%

% dx = linspace(0,tend,tend+1);

% dy = interp1(t,x,dx);

% Tv1 = table(dx',dy);

% writetable(Tv1,filename);

%

% for k=1:8 % forloop

% subplot(3,3,k), hold all %

% plot(t, x(:,k));

% xlabel('Time (min)')

% ylabel(ylabs(k))

% end

% end

Figure TTPpathway single cells

% filename = ('TablesTomidaTTP/TomidaTTP\_simulation\_20240701.csv');

% % AA/MK2i

% filename = ('TablesTomidaTTP/TomidaTTP\_AA\_simulation\_20240701.csv');

% phiT = 0;

% Tp0=0;

% % % EE (TTP = TTP phosphorylated)

% filename = ('TablesTomidaTTP/TomidaTTP\_EE\_simulation\_20240701.csv');

% phiT = 0;

% Tp0=0;

% deltaT = 0.0029; %0.0000001;

% deltaAm2 = 0;

% %DUSPKO

% filename = ('TablesTomidaTTP/TomidaTTP\_DUSPKO\_simulation\_20240701.csv');

% gammaD=0;

% D0=0;

% % % p38i

% filename = ('TablesTomidaTTP/TomidaTTP\_p38i\_simulation\_20240701.csv');gammaD=0;

% gammaAm=0;

% phiT=0;

% D0=0;

% Tp0=0;

% Am0=0;

% DUSP1i

filename = ('TablesTomidaTTP/TomidaTTP\_DUSPi\_simulation\_20240701.csv');

rhoPp=0;

% %PP2Ai

% filename = ('TablesTomidaTTP/TomidaTTP\_PP2Ai\_simulation\_20240701.csv');

% rhoTp = 0;

% T0=0;

% define figure labels

ylabs= {'p38';'p38-P';'dusp1 mRNA';'DUSP1';'TTP';'TTP-P';'TTP total';'TNF mRNA'};

[t,x] = ode23(@TTPpathway,[0 tend],x0,options,S,phiP,rhoPp,km,gammaDm,deltaDm,gammaD,deltaD,gammaT,deltaT,phiT,deltaTp,rhoTp,gammaAm,deltaAm1,deltaAm2);

% plot figure

for k=1:8 % forloop

 subplot(3,3,k), hold all %

 plot(t, x(:,k));

 xlabel('Time (min)')

 ylabel(ylabs(k))

end

hold off

%

dx = linspace(0,tend,tend+1);

dy = interp1(t,x,dx);

Tv1 = table(dx',dy);

writetable(Tv1,filename);

Function Tomida

function f=TTPpathway(t,x,S,phiP,rhoPp,km,gammaDm,deltaDm,gammaD,deltaD,gammaT,deltaT,phiT,deltaTp,rhoTp,gammaAm,deltaAm1,deltaAm2)

P = x(1);

Pp = x(2);

Dm = x(3);

D = x(4);

T = x(5);

Tp = x(6);

Tt = x(7);

Am = x(8);

% Differential equations Tomida

% equation eT(1)

Pdiff = -(phiP\*S\*P) + (rhoPp\*D\*Pp)/(km+Pp);

% equation eT(2)

Ppdiff= +(phiP\*S\*P) - (rhoPp\*D\*Pp)/(km+Pp);

% equation eT(3)

Dmdiff= (gammaDm\*Pp) - (deltaDm\*Dm);

% equation eT(4)

Ddiff= (gammaD\*Dm) - (deltaD\*D);

% Differential equations TTP

% equation eB(1)

Tdiff = (gammaT\*Pp) - (deltaT\*T) - (phiT\*T\*Pp) + (rhoTp\*Tp);

% equation eB(2)

Tpdiff = - (deltaTp\*Tp) + (phiT\*T\*Pp)- (rhoTp\*Tp);

%

Ttdiff = Tdiff + Tpdiff;

% equation eB(3)

Amdiff = (gammaAm\*Pp) - (deltaAm1\*Am) - (deltaAm2\*T\*Am);

f=[Pdiff Ppdiff Dmdiff Ddiff Tdiff Tpdiff Ttdiff Amdiff]';

end