%%

clear all

format long

clc

% construct vectors and set initial conditions

time=[0]; % time

c0=0.1; % resting calcium concentration

cb=c0; % initial microdomian calcium concentration

c=c0; % initial cytosolic calcium concentration

ct0=45; % total calcium concentration

ct=ct0;

gamma1=100;gamma2=10;

Num\_IPR=20; % number of IP3Rs

state=4\*ones(Num\_IPR,1); % number indicates the state in order (C1 C2 C3 C4 O5 O6)

cm=c(end)\*ones(Num\_IPR,1); % calcium concentration at each IP3R channel mouth

dt0=1e-4; % initial time stepsize in unit of second

dt=dt0;

g=zeros(Num\_IPR,1); % tracking variable for determining transition time

r1=rand(Num\_IPR,1); % uniform random variable on [0,1]

% IP3R parameters

q45=11;q54=3330;q12=1240;q21=88;q23=3;q32=69;q26=10500;q62=4010;

p=0.15; % IP3 concentration (muM)

V42=110\*p.^2./(p.^2+0.1^2);

k42=0.49+0.543\*p.^3./(p.^3+4^3);

n42=3;

kn42=0.41+25\*p.^3./(p.^3+6.5^3);

nn42=3;

a42=1.8\*p.^2./(p.^2+0.58^2);

V24=62+880./(p.^2+4);

k24=0.35;

n24=3;

kn24=80;

nn24=2;

a24=1+5./(p.^2+0.5^2);

% other model parameters (see main text for details)

Vs=10;

Ks=0.26;

kipr=0.05/Num\_IPR;

kleak=0.0032;

kdiff=10;

Vp=0.8;

Kp=0.5;

Jleakin=0.03115;

Vrocc=0.2;

Jrocc=Vrocc\*p;

Vsocc=1.6;

Ksocc=100;

h24\_inf=kn24^nn24./(kn24^nn24+c0.^nn24);

h24=h24\_inf\*ones(Num\_IPR,1);

h24\_new=h24;

lambda\_h24=40;

m24\_inf=c0.^n24./(k24^n24+c0.^n24);

m24=m24\_inf\*ones(Num\_IPR,1);

m24\_new=m24;

lambda\_m24=100;

m42\_inf=c0.^n42./(k42.^n42+c0.^n42);

m42=m42\_inf\*ones(Num\_IPR,1);

m42\_new=m42;

lambda\_m42=100;

h42\_inf=kn42^nn42./(kn42^nn42+c0.^nn42);

h42=h42\_inf\*ones(Num\_IPR,1);

h42\_new=h42;

h42\_track=h42;

ah42=0.5;

Vh42=20;

IT=1; % incremental time per iteration (s)

Numtimes=400; % number of iterations

% In the following, I will generate Numtimes files, each of which contain

% information connected in time. At last, I combine all the files in order

% to generate one file for analysis

wb=waitbar(0,'please wait...'); % show waitbar to indicate progress

for full=1:Numtimes

tic % record time spent for each iteration for user control

Tmax=IT\*full;

while time(end)<Tmax

 No=0; % No is the number of open channels

 for openind=1:Num\_IPR

 if state(openind,end)>=5

 No=No+1;

 end

 end

 % First using the preceding time step dt to update the system (initial estimation)

 Y0=[c(end);cb(end);ct(end)];

 % here use RK4 to solve the ODEs

 cs=gamma2\*(Y0(3)-Y0(2)/gamma1-Y0(1));

 Jdiff=kdiff\*(Y0(2)-Y0(1));

 Jleak=kleak\*(cs-Y0(1));

 Jserca=Vs\*Y0(1)^1.75/(Y0(1)^1.75+Ks^1.75);

 Jsocc=Vsocc\*Ksocc^4/(cs^4+Ksocc^4);

 Jin=Jleakin+Jrocc+Jsocc;

 Jpm=Vp\*Y0(1).^2./(0.5^2+Y0(1).^2);

 Jipr=kipr\*No\*(cs-Y0(2));

 YK1=dt\*[Jdiff+Jleak-Jserca+Jin-Jpm

 gamma1\*(Jipr-Jdiff)

 Jin-Jpm];

 Y1=Y0+YK1/2;

 cs=gamma2\*(Y1(3)-Y1(2)/gamma1-Y1(1));

 Jdiff=kdiff\*(Y1(2)-Y1(1));

 Jleak=kleak\*(cs-Y1(1));

 Jserca=Vs\*Y1(1)^1.75/(Y1(1)^1.75+Ks^1.75);

 Jsocc=Vsocc\*Ksocc^4/(cs^4+Ksocc^4);

 Jin=Jleakin+Jrocc+Jsocc;

 Jpm=Vp\*Y1(1).^2./(0.5^2+Y1(1).^2);

 Jipr=kipr\*No\*(cs-Y1(2));

 YK2=dt\*[Jdiff+Jleak-Jserca+Jin-Jpm

 gamma1\*(Jipr-Jdiff)

 Jin-Jpm];

 Y2=Y0+YK2/2;

 cs=gamma2\*(Y2(3)-Y2(2)/gamma1-Y2(1));

 Jdiff=kdiff\*(Y2(2)-Y2(1));

 Jleak=kleak\*(cs-Y2(1));

 Jserca=Vs\*Y2(1)^1.75/(Y2(1)^1.75+Ks^1.75);

 Jsocc=Vsocc\*Ksocc^4/(cs^4+Ksocc^4);

 Jin=Jleakin+Jrocc+Jsocc;

 Jpm=Vp\*Y2(1).^2./(0.5^2+Y2(1).^2);

 Jipr=kipr\*No\*(cs-Y2(2));

 YK3=dt\*[Jdiff+Jleak-Jserca+Jin-Jpm

 gamma1\*(Jipr-Jdiff)

 Jin-Jpm];

 Y3=Y0+YK3;

 cs=gamma2\*(Y3(3)-Y3(2)/gamma1-Y3(1));

 Jdiff=kdiff\*(Y3(2)-Y3(1));

 Jleak=kleak\*(cs-Y3(1));

 Jserca=Vs\*Y3(1)^1.75/(Y3(1)^1.75+Ks^1.75);

 Jsocc=Vsocc\*Ksocc^4/(cs^4+Ksocc^4);

 Jin=Jleakin+Jrocc+Jsocc;

 Jpm=Vp\*Y3(1).^2./(0.5^2+Y3(1).^2);

 Jipr=kipr\*No\*(cs-Y3(2));

 YK4=dt\*[Jdiff+Jleak-Jserca+Jin-Jpm

 gamma1\*(Jipr-Jdiff)

 Jin-Jpm];

 Y\_new=Y0+(YK1+2\*YK2+2\*YK3+YK4)/6;

 c\_new=Y\_new(1);

 cb\_new=Y\_new(2);

 ct\_new=Y\_new(3);

 dt1=dt\*ones(Num\_IPR,1);

 % update gating variables

 for i=1:Num\_IPR

 cs=gamma2\*(ct\_new(end)-cb\_new(end)/gamma1-c\_new(end));

 cm(i)=cb\_new\*heaviside(4.5-state(i,end))+120\*(cs/100)\*heaviside(state(i,end)-4.5);

 % updating m42

 m42\_inf=cm(i).^n42./(k42.^n42+cm(i).^n42);

 YK1=dt\*lambda\_m42\*(m42\_inf-m42(i));

 Y1=m42(i)+YK1/2;

 YK2=dt\*lambda\_m42\*(m42\_inf-Y1);

 Y2=m42(i)+YK2/2;

 YK3=dt\*lambda\_m42\*(m42\_inf-Y2);

 Y3=m42(i)+YK3;

 YK4=dt\*lambda\_m42\*(m42\_inf-Y3);

 m42\_new(i)=m42(i)+(YK1+2\*YK2+2\*YK3+YK4)/6;

 % updating h42

 h42\_inf=kn42^nn42./(kn42^nn42+cm(i).^nn42);

 lambda\_h42=ah42\*heaviside(4.5-state(i,end))+Vh42\*heaviside(state(i,end)-4.5);

 YK1=dt\*lambda\_h42\*(h42\_inf-h42(i));

 Y1=h42(i)+YK1/2;

 YK2=dt\*lambda\_h42\*(h42\_inf-Y1);

 Y2=h42(i)+YK2/2;

 YK3=dt\*lambda\_h42\*(h42\_inf-Y2);

 Y3=h42(i)+YK3;

 YK4=dt\*lambda\_h42\*(h42\_inf-Y3);

 h42\_new(i)=h42(i)+(YK1+2\*YK2+2\*YK3+YK4)/6;

 % updating m24

 m24\_inf=cm(i).^n24./(k24^n24+cm(i).^n24);

 YK1=dt\*lambda\_m24\*(m24\_inf-m24(i));

 Y1=m24(i)+YK1/2;

 YK2=dt\*lambda\_m24\*(m24\_inf-Y1);

 Y2=m24(i)+YK2/2;

 YK3=dt\*lambda\_m24\*(m24\_inf-Y2);

 Y3=m24(i)+YK3;

 YK4=dt\*lambda\_m24\*(m24\_inf-Y3);

 m24\_new(i)=m24(i)+(YK1+2\*YK2+2\*YK3+YK4)/6;

 % updating h24

 h24\_inf=kn24^nn24./(kn24^nn24+cm(i).^nn24);

 YK1=dt\*lambda\_h24\*(h24\_inf-h24(i));

 Y1=h24(i)+YK1/2;

 YK2=dt\*lambda\_h24\*(h24\_inf-Y1);

 Y2=h24(i)+YK2/2;

 YK3=dt\*lambda\_h24\*(h24\_inf-Y2);

 Y3=h24(i)+YK3;

 YK4=dt\*lambda\_h24\*(h24\_inf-Y3);

 h24\_new(i)=h24(i)+(YK1+2\*YK2+2\*YK3+YK4)/6;

 % the next step is to determine the transition time by linear interpolation

 q24=(a24+V24\*(1-m24(i).\*h24(i)));

 q42=a42+V42\*m42(i).\*h42(i);

 Ta\_old=[0 q12 0 0 0 0 ;q21 0 q23 q24 0 q26;0 q32 0 0 0 0;0 q42 0 0 q45 0;...

 0 0 0 q54 0 0;0 q62 0 0 0 0]; % old transition matrix

 q24=(a24+V24\*(1-m24\_new(i).\*h24\_new(i)));

 q42=a42+V42\*m42\_new(i).\*h42\_new(i);

 Ta\_new=[0 q12 0 0 0 0 ;q21 0 q23 q24 0 q26;0 q32 0 0 0 0;0 q42 0 0 q45 0;...

 0 0 0 q54 0 0;0 q62 0 0 0 0]; % new transition matrix

 g\_old=g(i);

 g\_new=g\_old+(sum(Ta\_old(state(i,end),:))+sum(Ta\_new(state(i,end),:)))/2\*dt; % trapezoid intergration

 epsilon=log(1/r1(i));

 if g\_new>=epsilon % transition occurs

 dt1(i)=(epsilon-g\_old)/(g\_new-g\_old)\*dt; % determine the transition time by linear interpolation

 end

 end

 [dt\_min index]=min(abs(dt1));

 if index==1 && dt\_min/dt==1

 index=0;

 end

 dt=dt\_min; % the found time interval from preceding time to transition time

 % Now reupdate the system again using the "true" dt.

 Y0=[c(end);cb(end);ct(end)];

 % here use RK4 to solve the ODEs

 cs=gamma2\*(Y0(3)-Y0(2)/gamma1-Y0(1));

 Jdiff=kdiff\*(Y0(2)-Y0(1));

 Jleak=kleak\*(cs-Y0(1));

 Jserca=Vs\*Y0(1)^1.75/(Y0(1)^1.75+Ks^1.75);

 Jsocc=Vsocc\*Ksocc^4/(cs^4+Ksocc^4);

 Jin=Jleakin+Jrocc+Jsocc;

 Jpm=Vp\*Y0(1).^2./(0.5^2+Y0(1).^2);

 Jipr=kipr\*No\*(cs-Y0(2));

 YK1=dt\*[Jdiff+Jleak-Jserca+Jin-Jpm

 gamma1\*(Jipr-Jdiff)

 Jin-Jpm];

 Y1=Y0+YK1/2;

 cs=gamma2\*(Y1(3)-Y1(2)/gamma1-Y1(1));

 Jdiff=kdiff\*(Y1(2)-Y1(1));

 Jleak=kleak\*(cs-Y1(1));

 Jserca=Vs\*Y1(1)^1.75/(Y1(1)^1.75+Ks^1.75);

 Jsocc=Vsocc\*Ksocc^4/(cs^4+Ksocc^4);

 Jin=Jleakin+Jrocc+Jsocc;

 Jpm=Vp\*Y1(1).^2./(0.5^2+Y1(1).^2);

 Jipr=kipr\*No\*(cs-Y1(2));

 YK2=dt\*[Jdiff+Jleak-Jserca+Jin-Jpm

 gamma1\*(Jipr-Jdiff)

 Jin-Jpm];

 Y2=Y0+YK2/2;

 cs=gamma2\*(Y2(3)-Y2(2)/gamma1-Y2(1));

 Jdiff=kdiff\*(Y2(2)-Y2(1));

 Jleak=kleak\*(cs-Y2(1));

 Jserca=Vs\*Y2(1)^1.75/(Y2(1)^1.75+Ks^1.75);

 Jsocc=Vsocc\*Ksocc^4/(cs^4+Ksocc^4);

 Jin=Jleakin+Jrocc+Jsocc;

 Jpm=Vp\*Y2(1).^2./(0.5^2+Y2(1).^2);

 Jipr=kipr\*No\*(cs-Y2(2));

 YK3=dt\*[Jdiff+Jleak-Jserca+Jin-Jpm

 gamma1\*(Jipr-Jdiff)

 Jin-Jpm];

 Y3=Y0+YK3;

 cs=gamma2\*(Y3(3)-Y3(2)/gamma1-Y3(1));

 Jdiff=kdiff\*(Y3(2)-Y3(1));

 Jleak=kleak\*(cs-Y3(1));

 Jserca=Vs\*Y3(1)^1.75/(Y3(1)^1.75+Ks^1.75);

 Jsocc=Vsocc\*Ksocc^4/(cs^4+Ksocc^4);

 Jin=Jleakin+Jrocc+Jsocc;

 Jpm=Vp\*Y3(1).^2./(0.5^2+Y3(1).^2);

 Jipr=kipr\*No\*(cs-Y3(2));

 YK4=dt\*[Jdiff+Jleak-Jserca+Jin-Jpm

 gamma1\*(Jipr-Jdiff)

 Jin-Jpm];

 Y\_new=Y0+(YK1+2\*YK2+2\*YK3+YK4)/6;

 c\_new=Y\_new(1);

 cb\_new=Y\_new(2);

 ct\_new=Y\_new(3);

 for i=1:Num\_IPR

 cs=gamma2\*(ct\_new(end)-cb\_new(end)/gamma1-c\_new(end));

 cm(i)=cb\_new\*heaviside(4.5-state(i,end))+120\*(cs/100)\*heaviside(state(i,end)-4.5);

 % updating m42

 m42\_inf=cm(i).^n42./(k42.^n42+cm(i).^n42);

 YK1=dt\*lambda\_m42\*(m42\_inf-m42(i));

 Y1=m42(i)+YK1/2;

 YK2=dt\*lambda\_m42\*(m42\_inf-Y1);

 Y2=m42(i)+YK2/2;

 YK3=dt\*lambda\_m42\*(m42\_inf-Y2);

 Y3=m42(i)+YK3;

 YK4=dt\*lambda\_m42\*(m42\_inf-Y3);

 m42\_new(i)=m42(i)+(YK1+2\*YK2+2\*YK3+YK4)/6;

 % updating h42

 h42\_inf=kn42^nn42./(kn42^nn42+cm(i).^nn42);

 lambda\_h42=ah42\*heaviside(4.5-state(i,end))+Vh42\*heaviside(state(i,end)-4.5);

 YK1=dt\*lambda\_h42\*(h42\_inf-h42(i));

 Y1=h42(i)+YK1/2;

 YK2=dt\*lambda\_h42\*(h42\_inf-Y1);

 Y2=h42(i)+YK2/2;

 YK3=dt\*lambda\_h42\*(h42\_inf-Y2);

 Y3=h42(i)+YK3;

 YK4=dt\*lambda\_h42\*(h42\_inf-Y3);

 h42\_new(i)=h42(i)+(YK1+2\*YK2+2\*YK3+YK4)/6;

 % updating m24

 m24\_inf=cm(i).^n24./(k24^n24+cm(i).^n24);

 YK1=dt\*lambda\_m24\*(m24\_inf-m24(i));

 Y1=m24(i)+YK1/2;

 YK2=dt\*lambda\_m24\*(m24\_inf-Y1);

 Y2=m24(i)+YK2/2;

 YK3=dt\*lambda\_m24\*(m24\_inf-Y2);

 Y3=m24(i)+YK3;

 YK4=dt\*lambda\_m24\*(m24\_inf-Y3);

 m24\_new(i)=m24(i)+(YK1+2\*YK2+2\*YK3+YK4)/6;

 % updating h24

 h24\_inf=kn24^nn24./(kn24^nn24+cm(i).^nn24);

 YK1=dt\*lambda\_h24\*(h24\_inf-h24(i));

 Y1=h24(i)+YK1/2;

 YK2=dt\*lambda\_h24\*(h24\_inf-Y1);

 Y2=h24(i)+YK2/2;

 YK3=dt\*lambda\_h24\*(h24\_inf-Y2);

 Y3=h24(i)+YK3;

 YK4=dt\*lambda\_h24\*(h24\_inf-Y3);

 h24\_new(i)=h24(i)+(YK1+2\*YK2+2\*YK3+YK4)/6;

 q24=(a24+V24\*(1-m24(i).\*h24(i)));

 q42=a42+V42\*m42(i).\*h42(i);

 Ta\_old=[0 q12 0 0 0 0;q21 0 q23 q24 0 q26;0 q32 0 0 0 0;0 q42 0 0 q45 0;...

 0 0 0 q54 0 0;0 q62 0 0 0 0];

 q24=(a24+V24\*(1-m24\_new(i).\*h24\_new(i)));

 q42=a42+V42\*m42\_new(i).\*h42\_new(i);

 Ta\_new=[0 q12 0 0 0 0;q21 0 q23 q24 0 q26;0 q32 0 0 0 0;0 q42 0 0 q45 0;...

 0 0 0 q54 0 0;0 q62 0 0 0 0];

 g(i)=g(i)+(sum(Ta\_old(state(i,end),:))+sum(Ta\_new(state(i,end),:)))/2\*dt; % update tracking variable

 end

 % add updated data to exsiting vectors

 c=[c,c\_new];

 cb=[cb,cb\_new];

 ct=[ct,ct\_new];

 time=[time,time(end)+dt];

 h24=h24\_new;

 m24=m24\_new;

 h42=h42\_new;

 h42\_track=[h42\_track,h42\_new];

 m42=m42\_new;

 % After finding the transition time and the channel that changes at the

 % time, now I determine which state the channel should enter.

 if index==0

 state=[state,state(:,end)];

 dt=dt0;

 else

 q24=(a24+V24\*(1-m24(index).\*h24(index)));

 q42=a42+V42\*m42(index).\*h42(index);

 Ta\_new=[0 q12 0 0 0 0 ;q21 0 q23 q24 0 q26;0 q32 0 0 0 0;0 q42 0 0 q45 0;...

 0 0 0 q54 0 0;0 q62 0 0 0 0];

 r2=rand; % uniform random variable on [0,1]

 previous=Ta\_new(state(index,end),:);

 kk=1;

 while sum(previous(1:kk))/sum(previous)<r2

 kk=kk+1;

 end

 current=state(:,end);

 current(index)=kk;

 state=[state,current];

 r1(index)=rand; % reset r1

 g(index)=0; % reset corresponding value of g back to zero

 end

end

toc

% save each interation

save(['6state\_Part\_',num2str(1000\*p),'\_',num2str(full)])

% update the variables used in the next interation

time=time(end);

c=c(end);

cb=cb(end);

ct=ct(end);

state=state(:,end);

h42\_track=h42\_track(:,end);

waitbar((full)/Numtimes)

end

close(wb) % close waitbar

%% this code is for gathering all the files made by the above code to generate a full file

totaltime=[]; % time

Ca=[]; % c values

Cab=[]; % cb values

CaT=[]; % ct values

h42\_total=[]; % h42

state\_total=[]; % state vector

wb1=waitbar(0,'please wait...');

for ldf=1:Numtimes

load(['6state\_Part\_',num2str(1000\*p),'\_',num2str(ldf)])

% gathering all the data

totaltime=[totaltime,time];

Ca=[Ca,c];

Cab=[Cab,cb];

CaT=[CaT,ct];

h42\_total=[h42\_total,h42\_track];

state\_total=[state\_total,state];

waitbar(ldf/Numtimes)

end

close(wb1)

% generate a MAT file for all the data

save(['Stochastic\_model\_6state\_IP3R\_model\_IP3\_',num2str(1000\*p),'nM\_total\_',num2str(Numtimes),'s'])

%% this file is for reducing the file size by decreasing the data resolution

% the quality of the reduced data set is still excellent for statistical analysis

clear B B\_new IT Jserca No Ta\_new Ta\_old Numtimes

clear Y0 Y1 Y2 Y3 YK1 YK2 YK3 YK4 Y\_new

clear c cb c\_new current cm dt1 dt\_min epsilon full g g\_new g\_old

clear h24 h24\_inf h24\_new h42 h42\_inf h42\_new h42\_track

clear m24 m24\_inf m24\_new m42 m42\_inf m42\_new

clear i index kk idf openind previous r1 r2 state time wb wb1

% decreasing resolution by a factor of 10.

c=Ca(1:10:end);

ct=CaT(1:10:end);

cb=Cab(1:10:end);

time=totaltime(1:10:end);

state=state\_total(:,1:10:end);

h42=h42\_total(:,1:10:end);

clear Ca Cab CaT totaltime state\_total h42\_total fluo

save(['Stochastic\_model\_6state\_IP3R\_model\_IP3\_',num2str(1000\*p),'nM\_total\_',num2str(Numtimes),'s\_smallversion'])