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ABSTRACT

Motivation

Result

Conclusion

1. INTRODUCTION

**2. MODELS AND SIMULATION RESULTS**

**The G1/S Model**

The mathematical model of the G1/S transition in mammalian cells is modified based on a previous model proposed by Kel et al. (2000) which includes a set of proteins and their regulatory gene factors. The schematic diagram of the G1/S transition network is provided in Figure X and their relationship is presented as differential equations provided in the supplementary material section [ref].

The level of E2F-1 is regulated by both cyclin D and cyclin E. At beginning of the cell cycle, E2F-1 is bound to the tumor suppressor (pRB). The activated cyclinD-cdk4,6 complex first promote the phosphorylation of pRB and then the activated cyclinE/CDK2 complex promote the reaction of double-phosphorylated pRB from to fully release E2F-1 [4]. Moreover, E2F-1 will amplify the signal of the generation of cyclin D, cyclin E, and pRB and cause them to reach a higher steady state.

**Modified model to show cell proliferation oscillation**

The pRB and the phosphorylated pRb will inhibit the cyclin D and cyclin E from being activated. The corresponding differential equations will be solved in Matlab to analyze its dynamic behavior.

**Overexpression of Cyclins and the resulted transcritical bifurcations**

It has been found that the strength of the mitogenic stimulation, Fm, serves as a significant bifurcation parameter affecting whether the cell will proliferate or not in the previous research [ref]. The sudden increase of the protein concentration indicates cell proliferation because high concentration of E2F1 is able to activate transcription of genes involved in S phase activities including DNA polymerase and thymidine kinase [ref]. The simulation output from the model shown in Figure X. below performs the time course of protein concentration at G1/S transition with different Fm values. It is observed that these protein concentrations will have bistability when Fm is greater than the transcritical bifurcation (TC) around 0.0035. The study was further extended to evaluate the change of transcritical bifurcation point when overexpressed the cyclin E, cyclinD, and combination by increasing their constitutive concentration.



Figure 1. Time course of the computed protein concentration with different strength of Fm, 0.00005 to 0.004 with an interval of 0.00005.

As the cyclin E is overexpressed by adding a constitutive concentration of 0.2 in the model, it is clearly seen that the transcritical bifurcation value become smaller as the bistability phenomenon observed in the earlier graphs shown in figure Y.



Figure 2. Time course of the computed protein concentration with the overexpresstion of cyclin E at the same value of Fm being tested above

It can be found that the effect of overexpressed cyclin D for cell proliferation is much greater than cyclin E that it shift the transcritical bifurcation to much smaller shown in figure Z blow. Figure ZZ. shows the combination effect form overexpression cyclin D and cyclin E, the E2F almost raise to the second stability at the beginning.





**Bifurcation for the Various Constitutive Concentrations**

The bifurcation diagram





CONCLUSIONS

ACKNOWLEDGEMENTS

**G1S\_Func**

function dydt=G1S\_Func(t,y,pars)

RB = y(1);

E2F = y(2);

CycD = y(3);

CycD\_a = y(4);

AP = y(5);

RB1 = y(6);

RB2 = y(7);

CycE = y(8);

CycE\_a = y(9);

k1 = pars(1);

k2 = pars(2);

k3 = pars(3);

k16 = pars(4);

k34 = pars(5);

k43 = pars(6);

k61 = pars(7);

k67 = pars(8);

k76 = pars(9);

k23 = pars(10);

k25 = pars(11);

k28 = pars(12);

k89 = pars(13);

k98 = pars(14);

a = pars(15);

J11 = pars(16);

J12 = pars(17);

J15 = pars(18);

J18 = pars(19);

J61 = pars(20);

J62 = pars(21);

J65 = pars(22);

J68 = pars(23);

J13 = pars(24);

J63 = pars(25);

Km1 = pars(26);

Km2 = pars(27);

Km4 = pars(28);

Km9 = pars(29);

kp = pars(30);

phi\_RB = pars(31);

phi\_E2F = pars(32);

phi\_CycD = pars(33);

phi\_CycD\_a = pars(34);

phi\_AP = pars(35);

phi\_RB1 = pars(36);

phi\_RB2 = pars(37);

phi\_CycE = pars(38);

phi\_CycE\_a = pars(39);

Fm = pars(40);

C=pars(41); %Constitutive Term

dydt(1,1) = k1\*E2F\*J11\*J61/((Km1+E2F)\*(J11+RB)\*(J61+RB1))-k16\*RB\*CycD\_a+k61\*RB1-phi\_RB\*RB;

dydt(2,1) = kp+k2\*(a^2+E2F^2)\*J12\*J62/((Km2^2+E2F^2)\*(J12+RB)\*(J62+RB1))-phi\_E2F\*E2F;

dydt(3,1) = k3\*AP+k23\*E2F\*J13\*J63/((J13+RB)\*(J63+RB1))+k43\*CycD\_a-k34\*CycD\*CycD\_a/(Km4+CycD\_a)-phi\_CycD\*CycD;

dydt(4,1) = k34\*CycD\*CycD\_a/(Km4+CycD\_a)-k43\*CycD\_a-phi\_CycD\_a\*CycD\_a;

dydt(5,1) = Fm + k25\*E2F\*J15\*J65/((J15+RB)\*(J65+RB1))-phi\_AP\*AP;

dydt(6,1) = k16\*RB\*CycD\_a-k61\*RB1-k67\*RB1\*CycE\_a+k76\*RB2-phi\_RB1\*RB1;

dydt(7,1) = k67\*RB1\*CycE\_a-k76\*RB2-phi\_RB2\*RB2;

dydt(8,1) = C+k28\*E2F\*J18\*J68/((J18+RB)\*(J68+RB1))+k98\*CycE\_a-k89\*CycE\*CycE\_a/(Km9+CycE\_a)-phi\_CycE\*CycE;

dydt(9,1) = k89\*CycE\*CycE\_a/(Km9+CycE\_a)-k98\*CycE\_a-phi\_CycE\_a\*CycE\_a;

end

**G1S\_Drive\_Bifurcation**

clc

clear all;

close all;

tspan = 0:1:1000;

%k1 k2 k3 k16 k34 k43 k61 k67 k76 k23 k25 k28 k89 k98 a

k=[1 1.6 0.05 0.4 0.04 0.01 0.30 0.7 0.1 0.3 0.9 0.06 0.07 0.01 0.04];

%J11 J12 J15 J18 J61 J62 J65 J68 J13 J63

J=[0.5 5.00 0.001 0.6 5.0 8.0 6.0 7 0.002 2.0];

%Km1 Km2 Km4 Km9 kp

Km=[0.5 4.0 0.3 0.005 0.05];

%phiRB phiE2F phicycD phicycDa phiAP phiPRBp phiPRBpp phiCycE phiCyca Fm

phi=[0.005 0.1 0.02300 0.030000 0.0100 0.06000 0.040000 0.06000 0.05000 0.044];

C=0;

pars = [k J Km phi C];

initial = [5 0 0 0.01 0 0 0 0 0.01];

figure;

%Solve for ODE at different Fm

for i=1:16

pars(40)=i\*0.0005;

options = odeset('reltol',1e-6);

[t,result{i}]=ode45(@G1S\_Func,tspan,initial,options,pars);

subplot(4,4,i);plot(t,result{i}); axis([0 1000 0 15]);

end

r1=result{1};r2=result{2};r3=result{3};r4=result{4};r5=result{5};

r6=result{6};r7=result{7};r8=result{8};r9=result{9};r10=result{10};

r11=result{11};r12=result{12};r13=result{13};r14=result{14};r15=result{15};r16=result{16};

Stability\_Low=[r1(200,2),r2(200,2),r3(200,2),r4(200,2),r5(200,2),r6(200,2),r7(200,2),r8(200,2),r9(200,2),r10(200,2),r11(200,2),r12(200,2),r13(200,2),r14(200,2),r15(200,2),r16(200,2)];

Stability\_High=[r1(800,2),r2(800,2),r3(800,2),r4(800,2),r5(800,2),r6(800,2),r7(800,2),r8(800,2),r9(800,2),r10(800,2),r11(800,2),r12(800,2),r13(800,2),r14(800,2),r15(800,2),r16(800,2)];

Fm=zeros(1,16);

for i=1:16

Fm(i)=i\*0.0005;

end

%Constitutive Overspression of Cyclin E

C=0.2;

k(12)=0.04;

pars = [k J Km phi C];

figure;

for i=1:16

pars(40)=i\*0.0005;

options = odeset('reltol',1e-6);

[t,result{i}]=ode45(@G1S\_Func,tspan,initial,options,pars);

subplot(4,4,i);plot(t,result{i}); axis([0 1000 0 15]);

end

r1=result{1};r2=result{2};r3=result{3};r4=result{4};r5=result{5};

r6=result{6};r7=result{7};r8=result{8};r9=result{9};r10=result{10};

r11=result{11};r12=result{12};r13=result{13};r14=result{14};r15=result{15};r16=result{16};

Stability\_Low1=[r1(200,2),r2(200,2),r3(200,2),r4(200,2),r5(200,2),r6(200,2),r7(200,2),r8(200,2),r9(200,2),r10(200,2),r11(200,2),r12(200,2),r13(200,2),r14(200,2),r15(200,2),r16(200,2)];

Stability\_High1=[r1(800,2),r2(800,2),r3(800,2),r4(800,2),r5(800,2),r6(800,2),r7(800,2),r8(800,2),r9(800,2),r10(800,2),r11(800,2),r12(800,2),r13(800,2),r14(800,2),r15(800,2),r16(800,2)];

%Generate Bifurcation plot

figure; axis([0 0.0005\*16 0 15]);

subplot(2,1,1);plot(Fm,Stability\_Low,Fm(7:16),Stability\_High(7:16));

xlabel('Fm');ylabel('E2F1');grid on;title('Bifurcation without Overexpression of Cyclin E')

subplot(2,1,2);plot(Fm,Stability\_Low1,Fm(4:16),Stability\_High1(4:16));

xlabel('Fm');ylabel('E2F1');grid on;title('Bifurcation with Overexpression of Cyclin E at C=0.2')

SUPPLEMENTARY MATERIALS

Original case









When C=0.2, K28=0.4







When C=0.4, K28=0.2





When D=0.02, k23=0.28



REFERENCES 