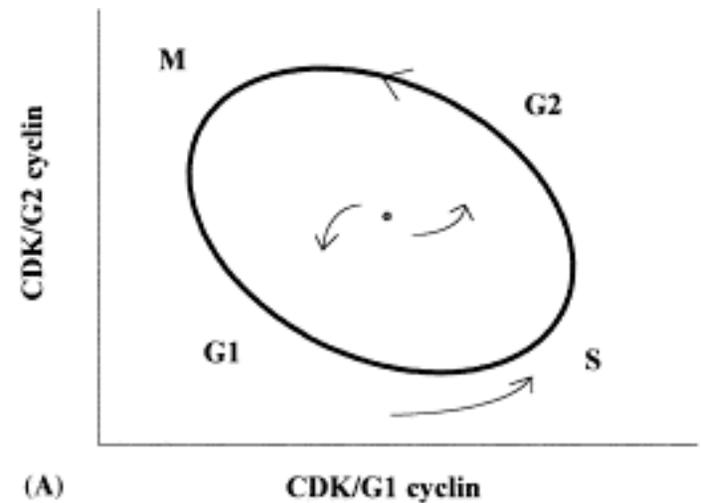
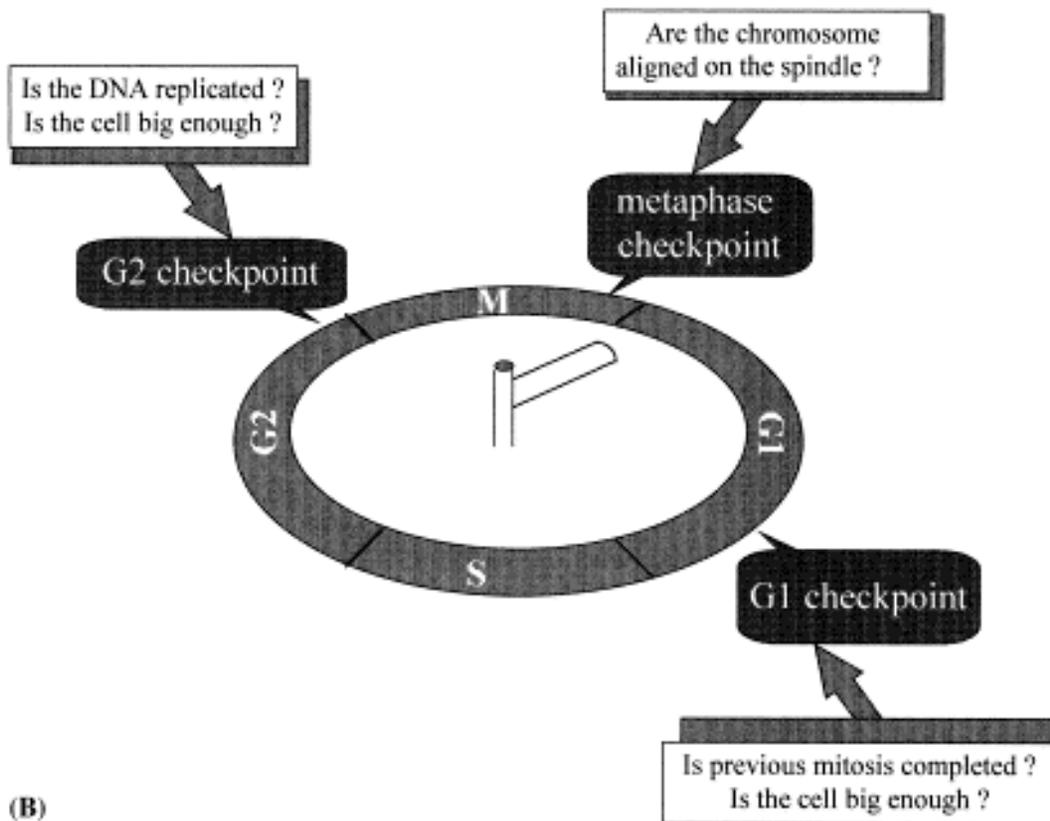
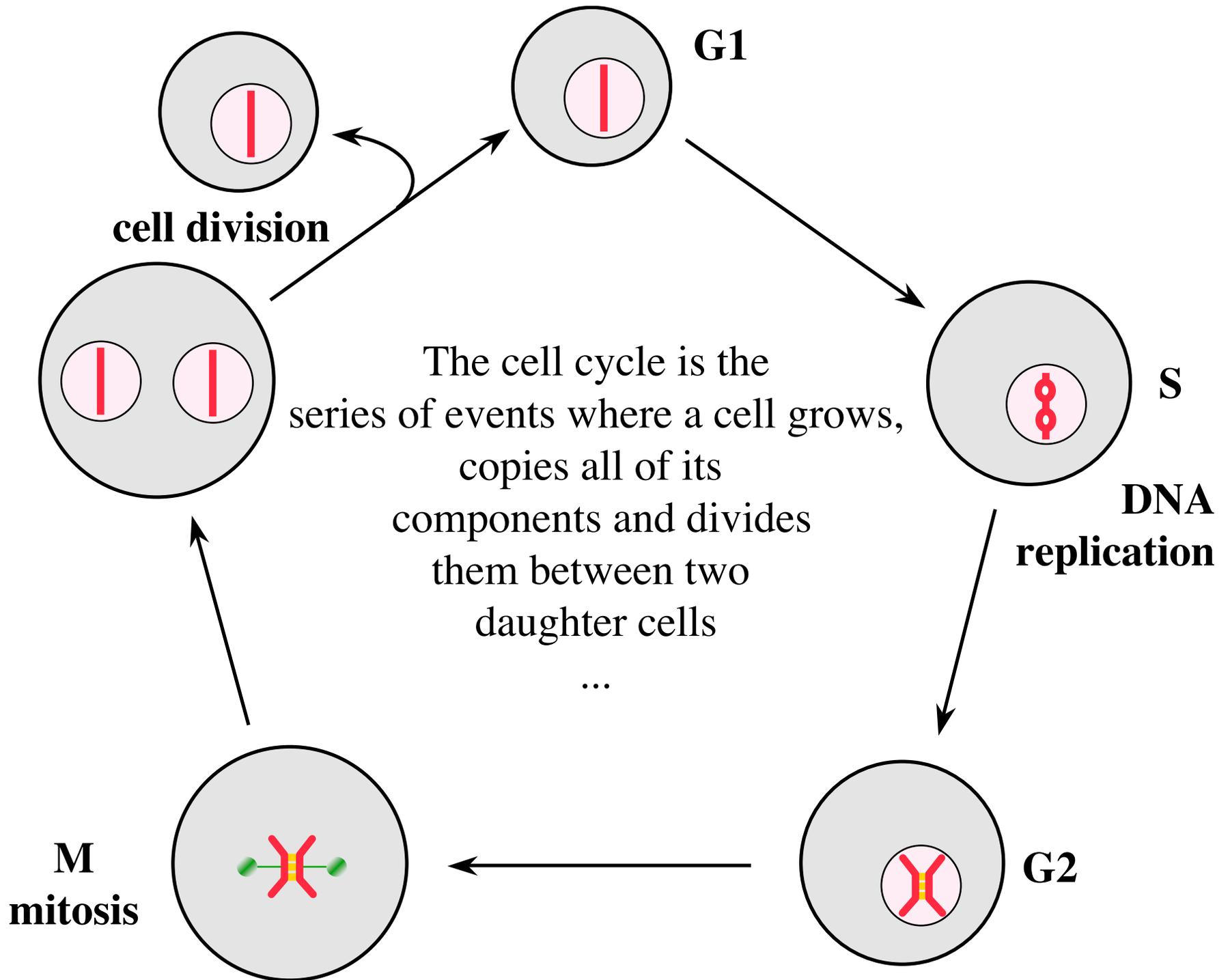


Cell cycle checkpoints



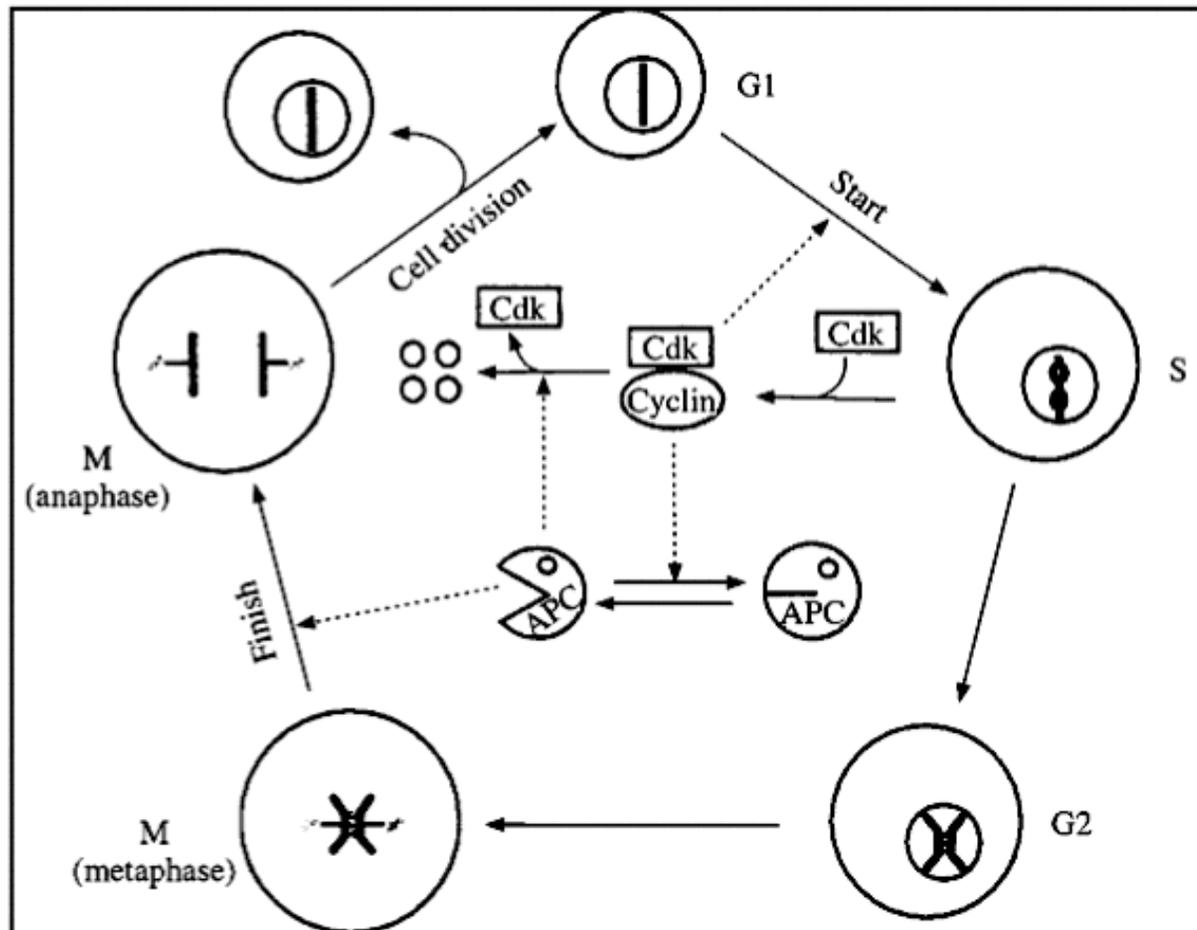
(B)

(A)

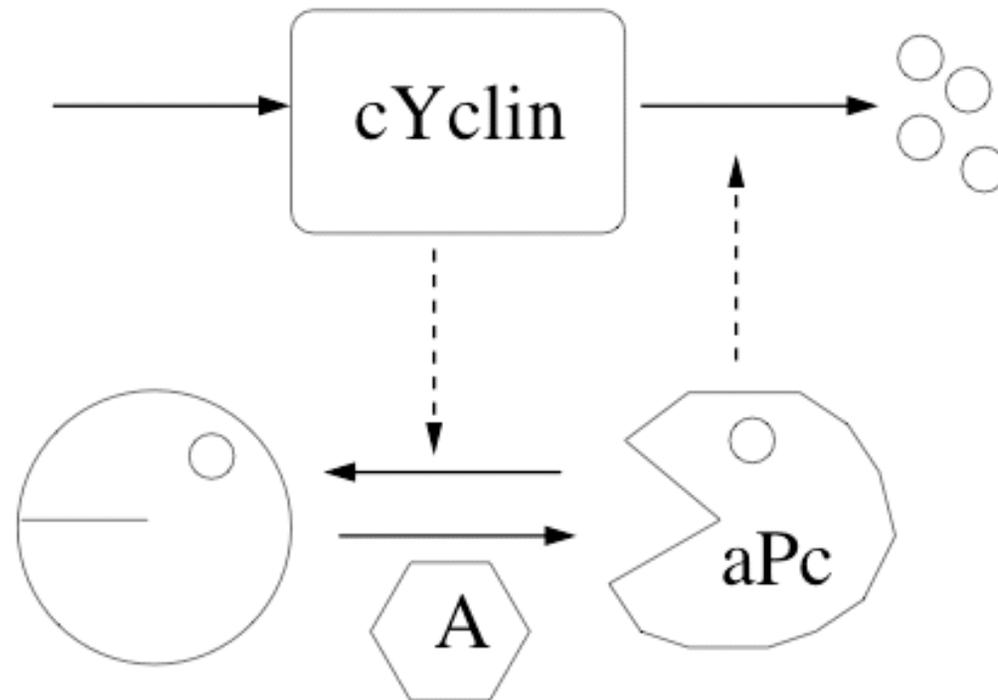


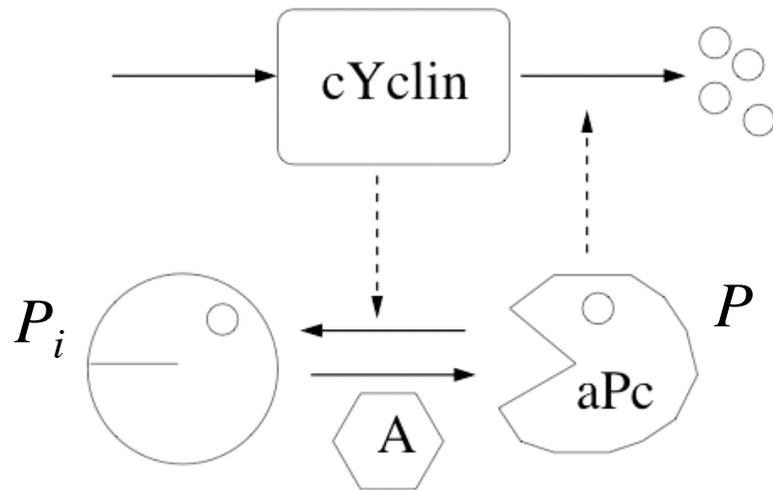
Simplified model (Cdk-cyclin vs APC complex)

Tyson & Novak JTB (2001)



'Toy model' for cYclin and aPc





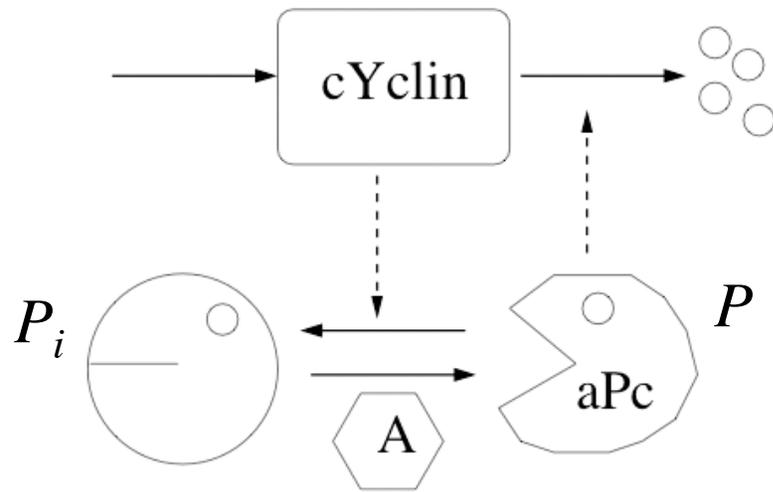
ODE's

Y=[Cyc] = cyclin cdk dimers
P= APC Cdh1 complex

This is the simplest model for switching between G1 and (S/G2/M)

$$Y' = k_1 - (k_{2p} + k_{2pp}P)Y$$

$$P' = \frac{V_i P_i}{J_3 + P_i} - \frac{V_a P}{J_4 + P}$$



ODE's

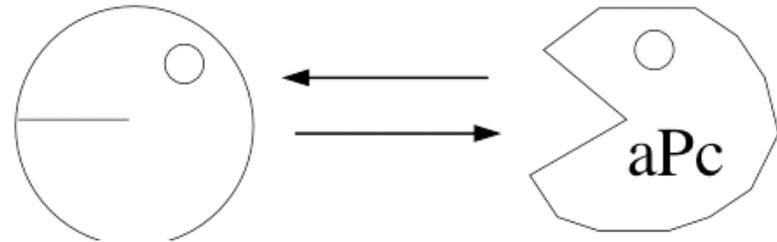
$$Y' = k_1 - (k_{2p} + k_{2pp}P)Y$$

$$P' = \frac{V_i P_i}{J_3 + P_i} - \frac{V_a P}{J_4 + P}$$

$$V_i = (k_{3p} + k_{3pp}A), \quad V_a = k_4 m Y$$

Assume total aPc constant

$$P + P_i = 1$$



Eliminate P_i

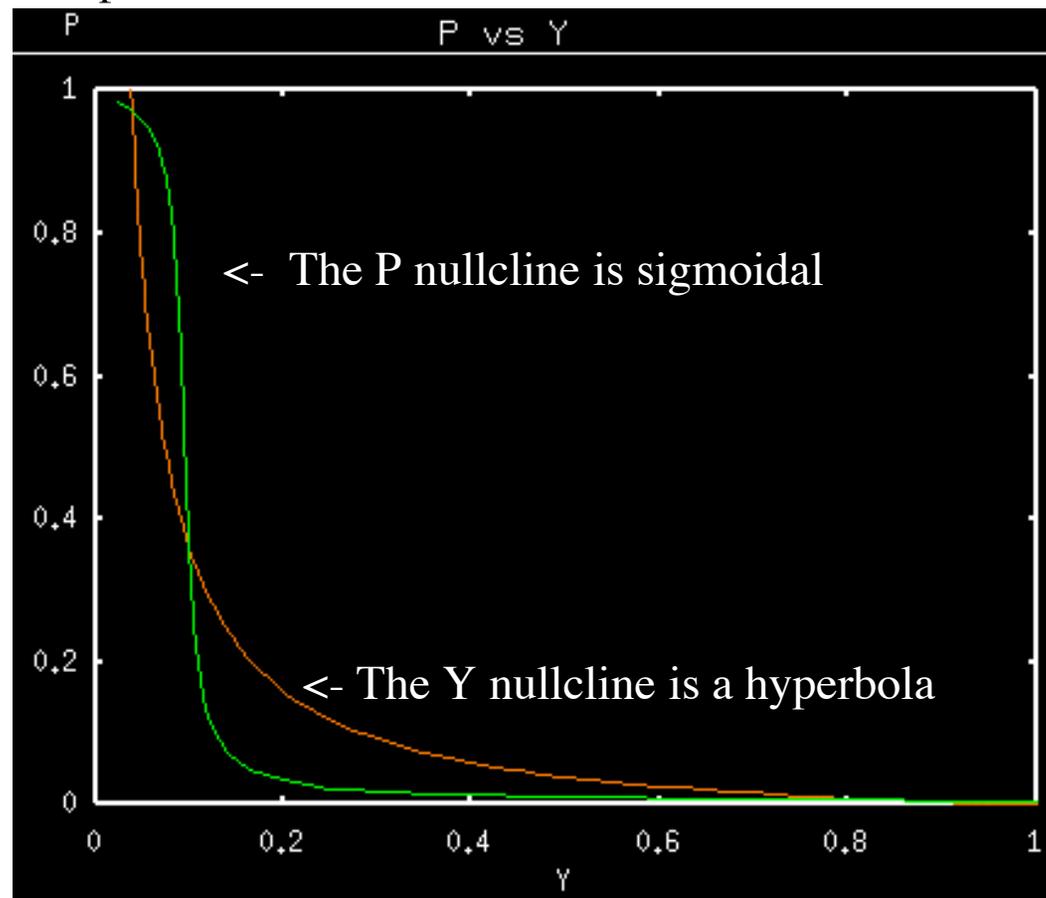
$$Y' = k_1 - (k_{2p} + k_{2pp}P)Y$$
$$P' = \frac{(k_{3p} + k_{3pp}A)(1 - P)}{J_3 + (1 - P)} - k_4m \frac{YP}{J_4 + P}$$

This is the system to be studied in the YP plane.

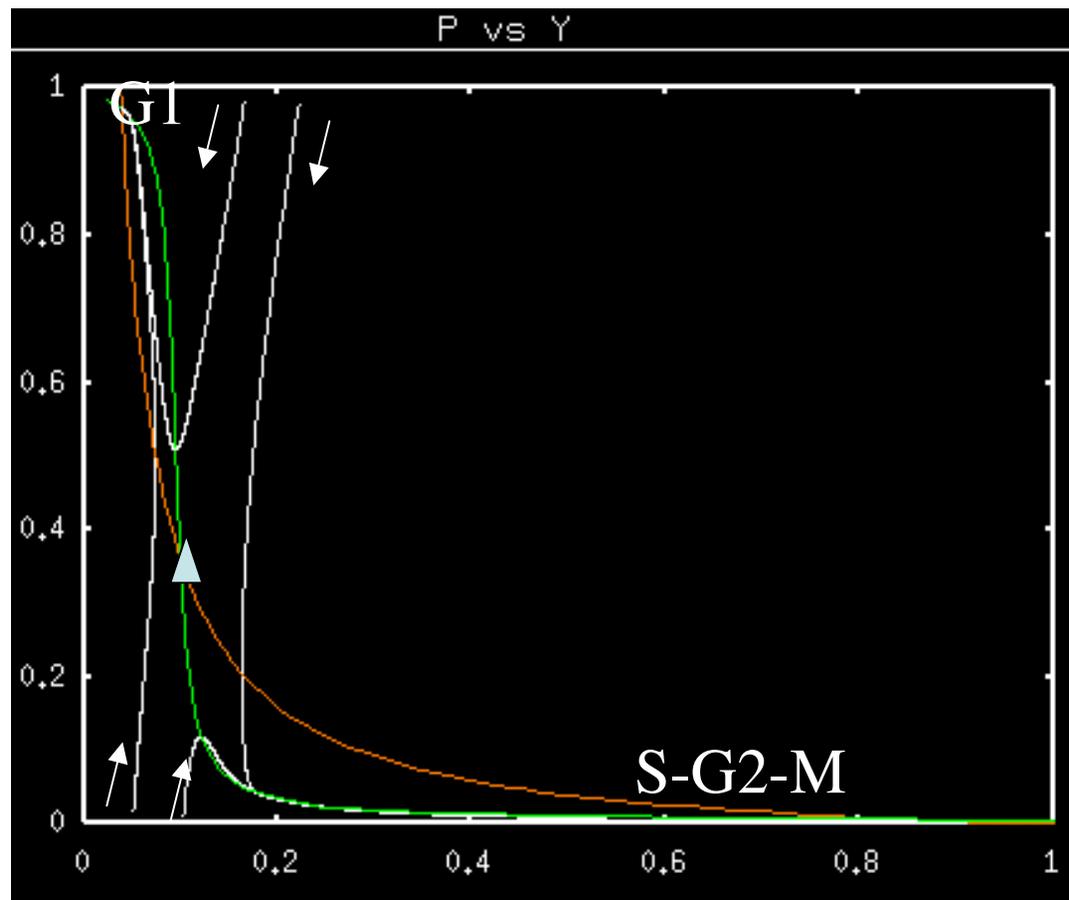
Phase portrait

$Y=[CycB]$ = cyclin cdk dimers

$P=[Cdh1]$ = APC Cdh1 complex



Switching behaviour

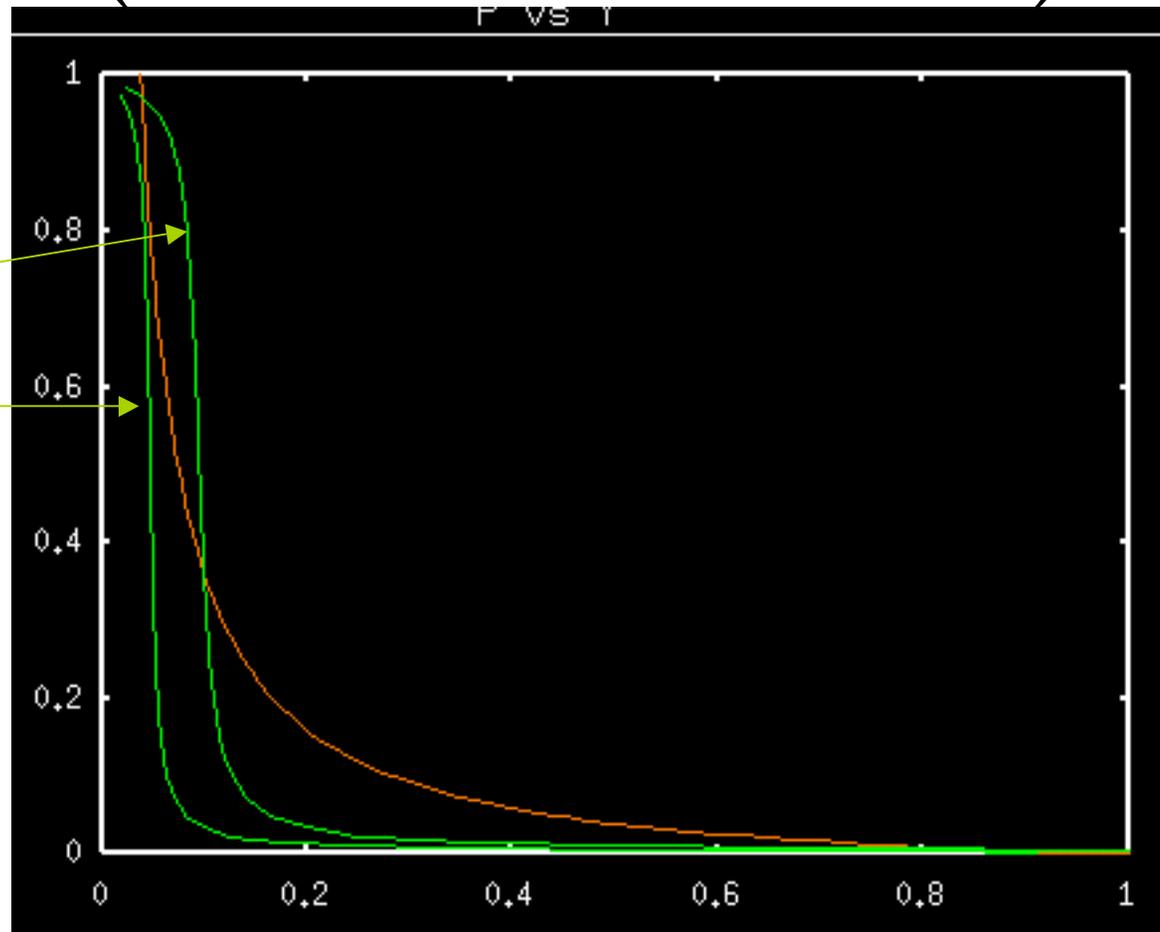


Change in behaviour as the cell grows (cell mass increases)

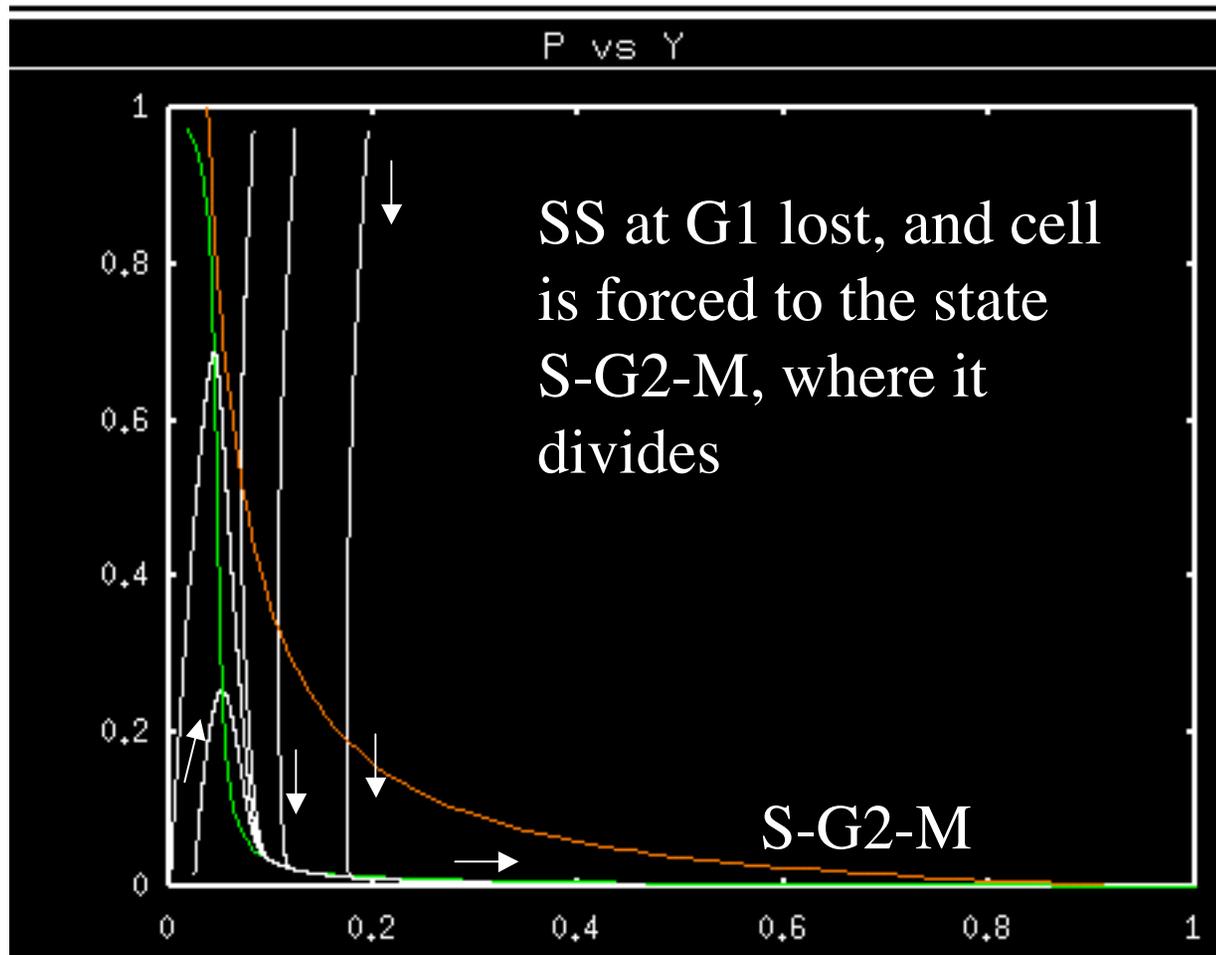
Cell mass

$m=0.3$

$m=0.6$



For larger mass:



Bifurcation

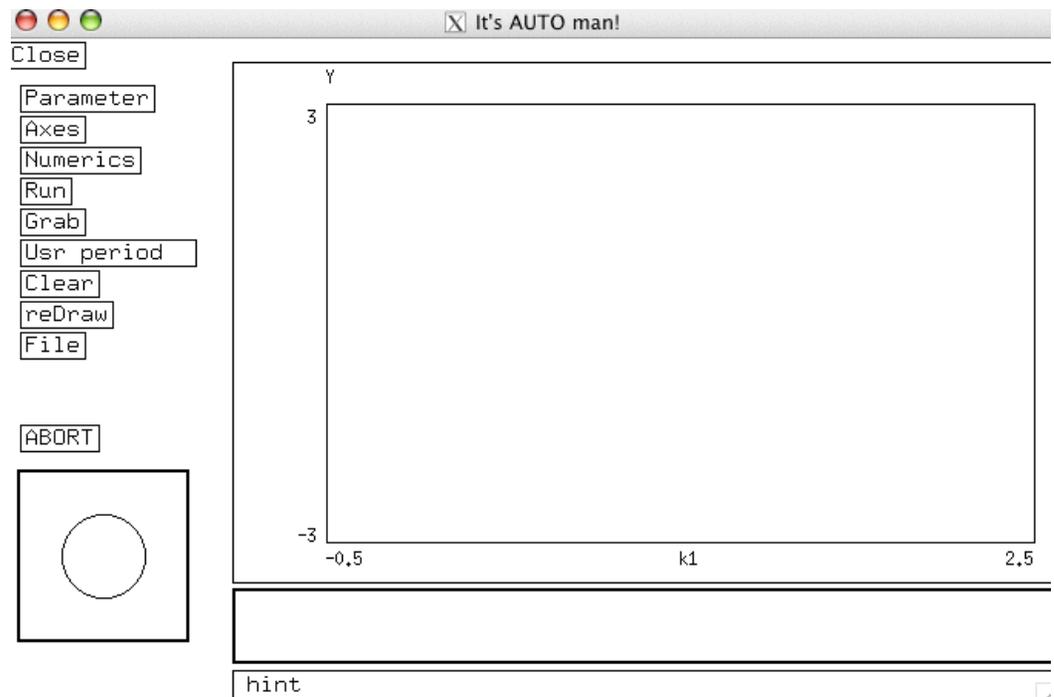
XPP Auto can be used to produce a bifurcation diagram that shows the number of steady states and how this depends on cell mass.

From XPP

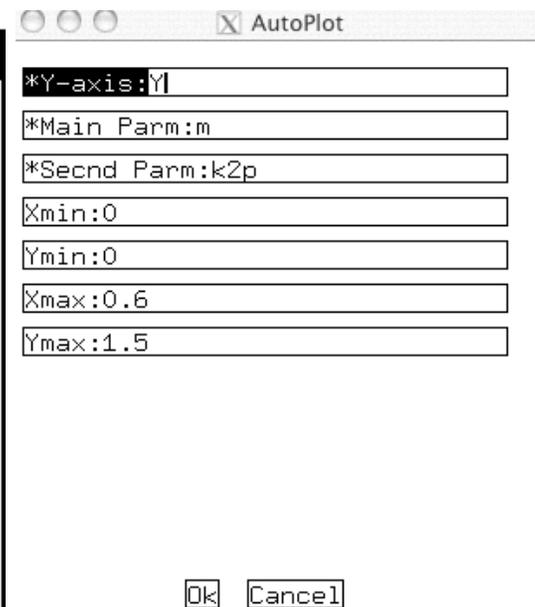
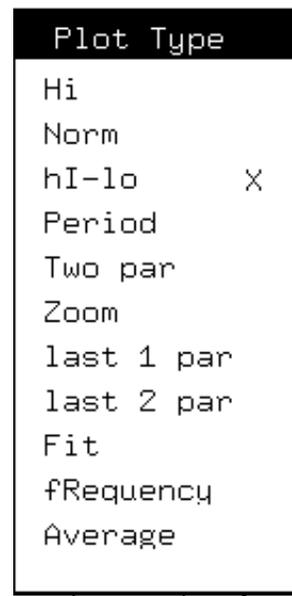
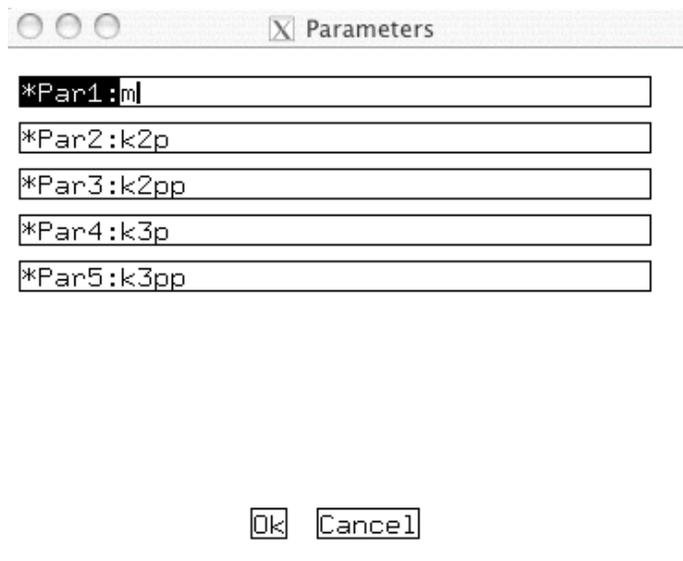
Click:

File

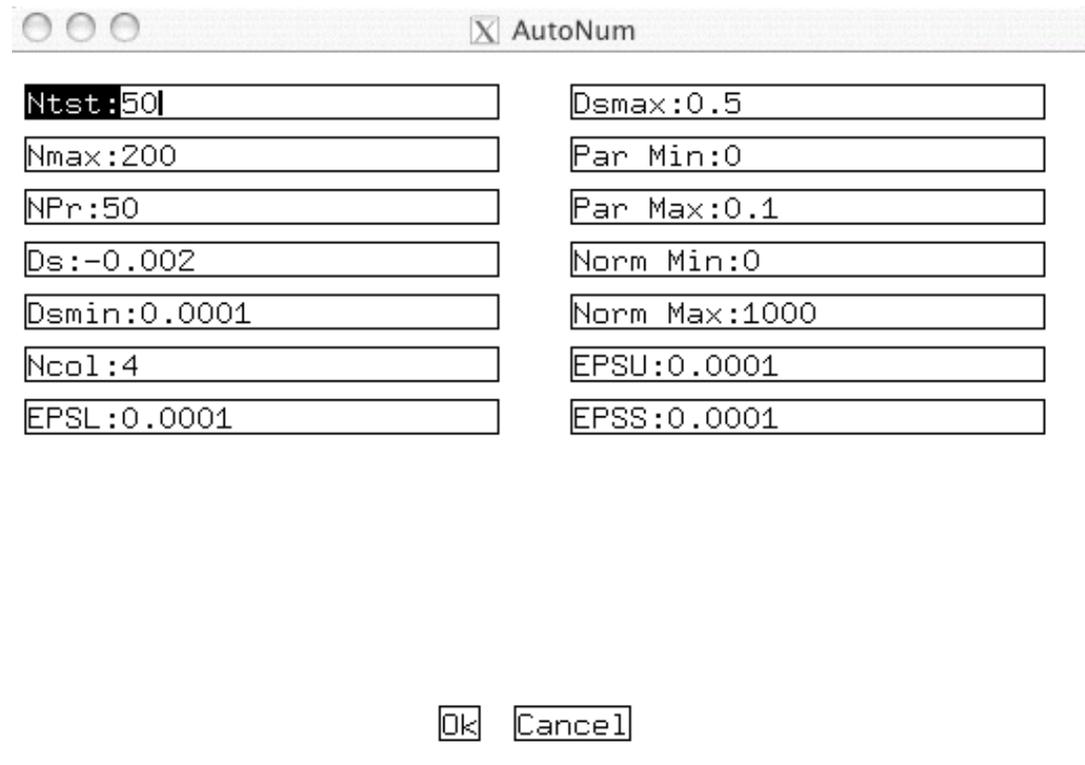
Auto



Auto Windows



Choosing some numerics

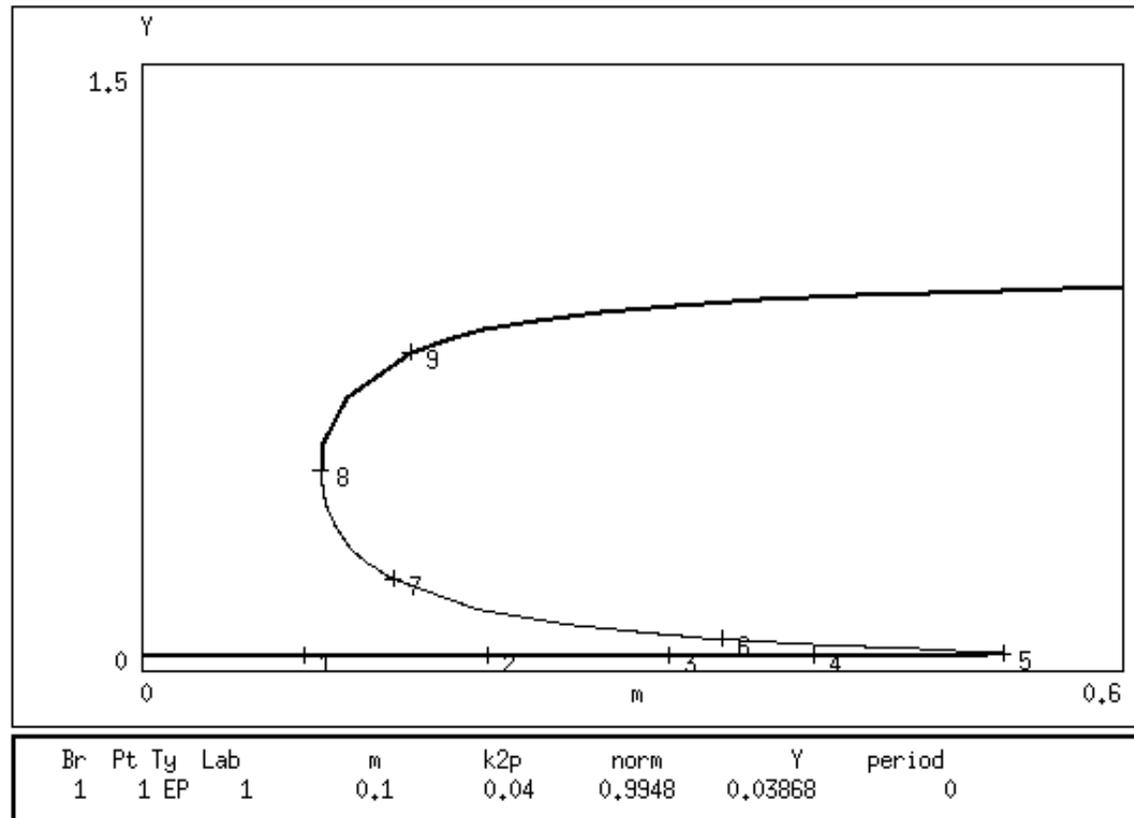


The image shows a dialog box titled "AutoNum" with a close button (X) in the top right corner. The dialog contains two columns of text input fields. The first column contains: "Ntst:50", "Nmax:200", "NPr:50", "Ds:-0.002", "Dsmin:0.0001", "Ncol:4", and "EPSL:0.0001". The second column contains: "Dsmax:0.5", "Par Min:0", "Par Max:0.1", "Norm Min:0", "Norm Max:1000", "EPSU:0.0001", and "EPSS:0.0001". At the bottom of the dialog, there are two buttons: "Ok" and "Cancel".

Ntst:50	Dsmax:0.5
Nmax:200	Par Min:0
NPr:50	Par Max:0.1
Ds:-0.002	Norm Min:0
Dsmin:0.0001	Norm Max:1000
Ncol:4	EPSU:0.0001
EPSL:0.0001	EPSS:0.0001

Ok Cancel

Auto bifurcation diagram



```
xterm
BR  PT TY LAB  PAR(1)  L2-NORM  U(1)  U(2)
1   7  EP  4  4.121716E-01  9.499959E-01  4.043938E-02  9.491348E-01

BR  PT TY LAB  PAR(1)  L2-NORM  U(1)  U(2)
1  10  LP  5  5.273193E-01  8.292318E-01  4.608560E-02  8.279502E-01
1  16  EP  6  3.557314E-01  4.580537E-01  8.150902E-02  4.507432E-01

BR  PT TY LAB  PAR(1)  L2-NORM  U(1)  U(2)
1  10  EP  7  1.543834E-01  2.659616E-01  2.296214E-01  1.341998E-01

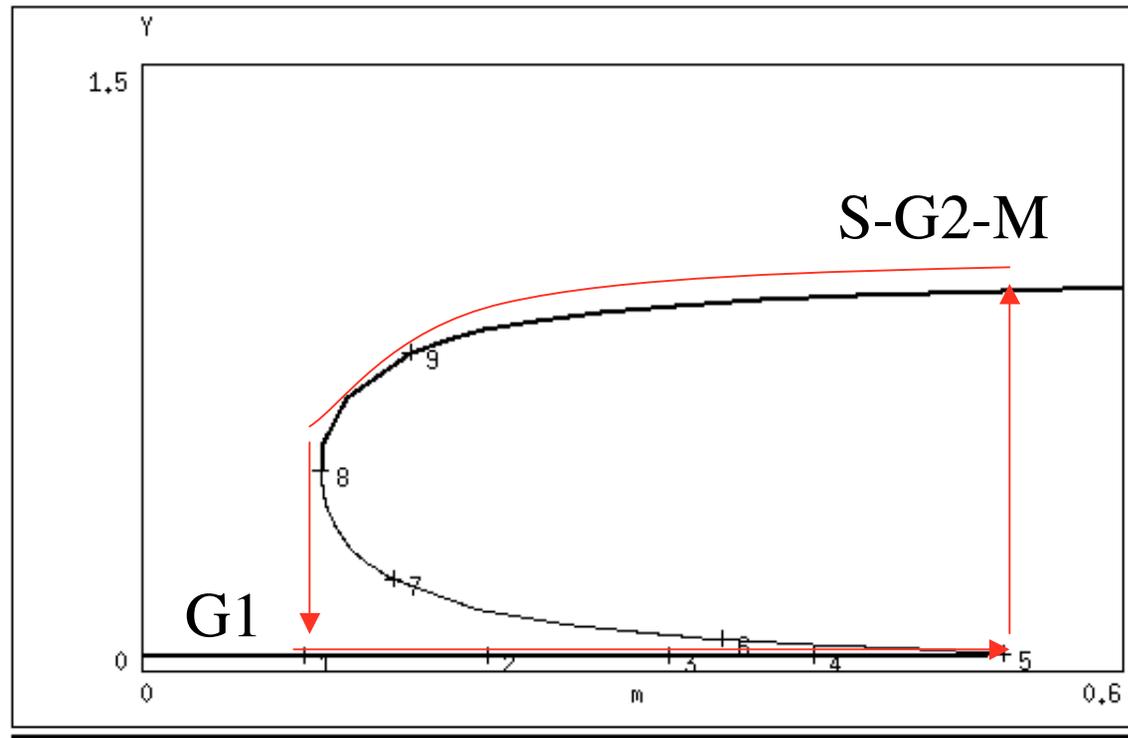
BR  PT TY LAB  PAR(1)  L2-NORM  U(1)  U(2)
1  11  LP  8  1.097140E-01  5.007662E-01  4.991552E-01  4.013540E-02
1  14  EP  9  1.645729E-01  7.884088E-01  7.883356E-01  1.073981E-02

BR  PT TY LAB  PAR(1)  L2-NORM  U(1)  U(2)
1  14  EP  10  6.587050E-01  9.563964E-01  9.563947E-01  1.823738E-03

BR  PT TY LAB  PAR(1)  L2-NORM  U(1)  U(2)
1   7  EP  11 -2.778588E-02  1.002123E+00  3.841031E-02  1.001387E+00

Eigenvalues:
```

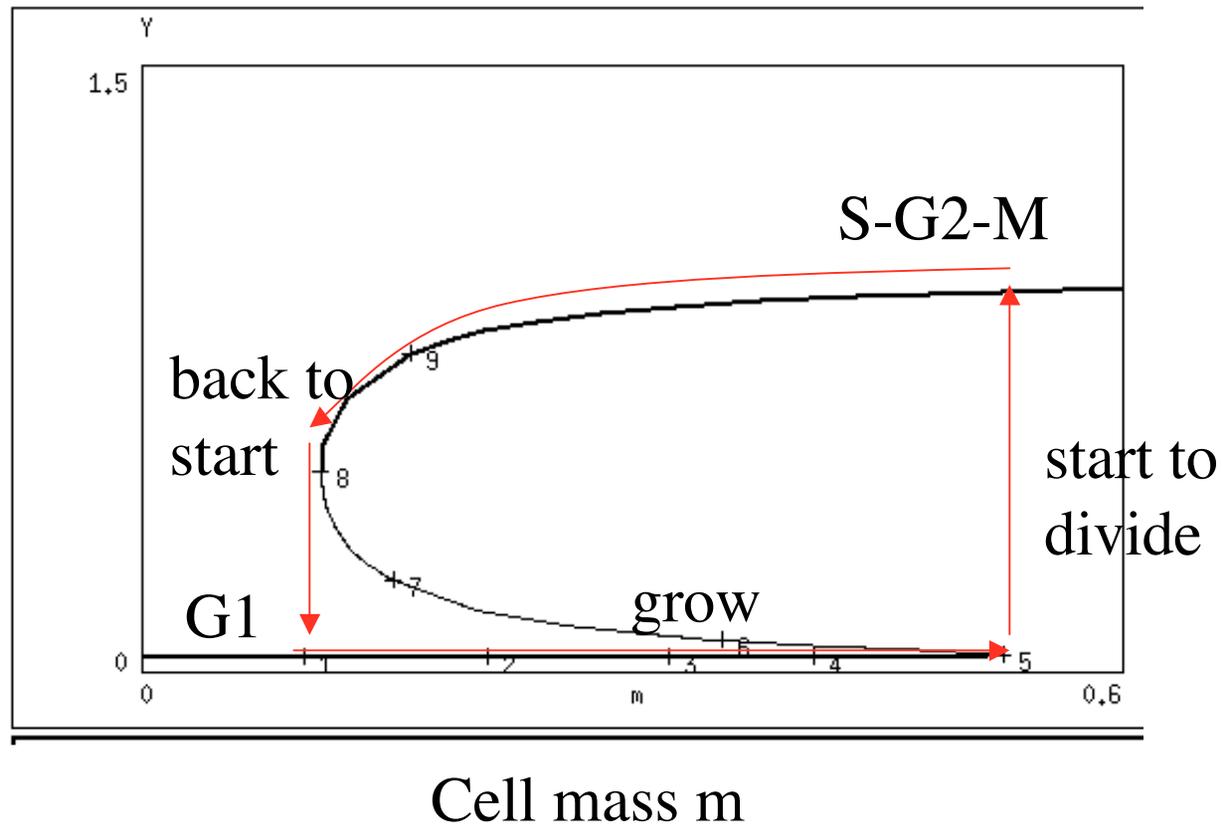
cyclin

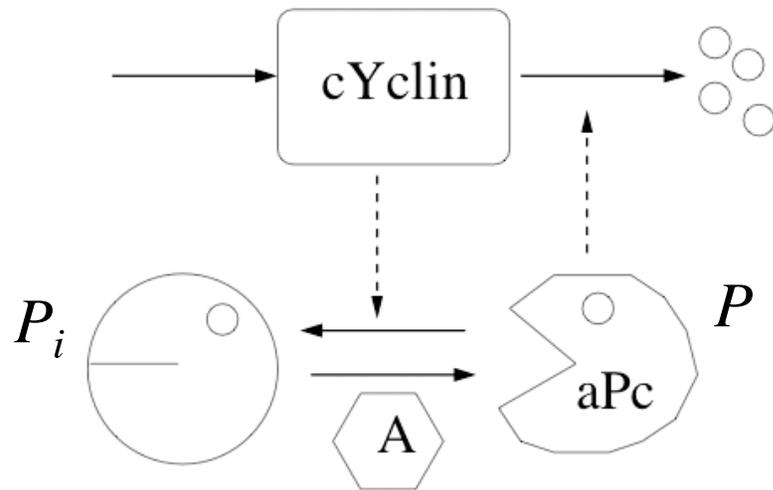


Cell mass m

The cell cycle

cyclin





Include A

$Y = [\text{Cyc}] = \text{cyclin cdk dimers}$
 $P = \text{APC Cdh1 complex}$
 $A = \text{Cdc20, the activator of aPc}$

$$Y' = k_1 - (k_{2p} + k_{2pp}P)Y$$

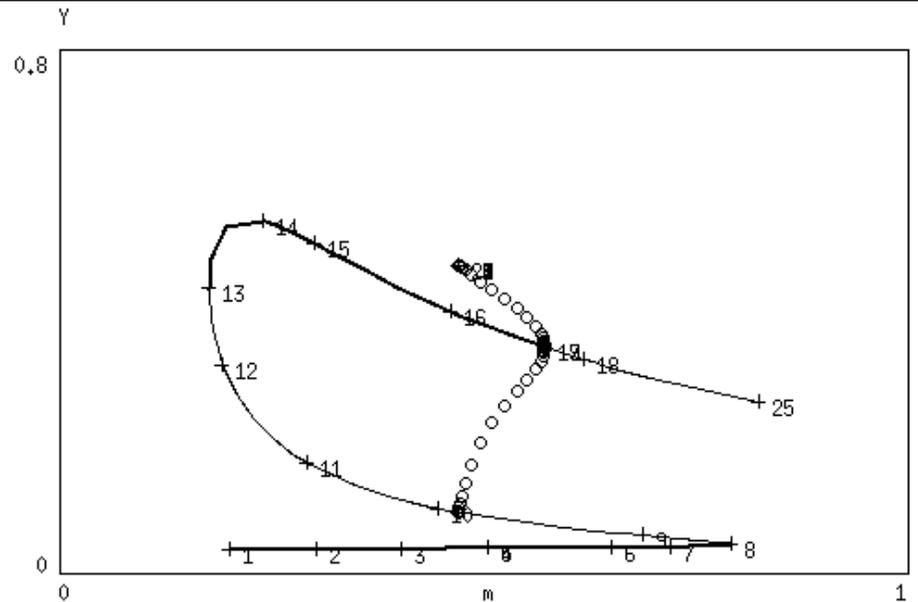
$$P' = \frac{(k_{3p} + k_{3pp}A)(1 - P)}{J_3 + (1 - P)} - k_4m \frac{YP}{J_4 + P}$$

$$A' = k_{5p} + k_{5pp} \frac{(mY/J_5)^n}{1 + (Ym/J_5)^n} - k_6A$$

$$Y' = k_1 - (k_2 p + k_2 p p * P) * Y$$

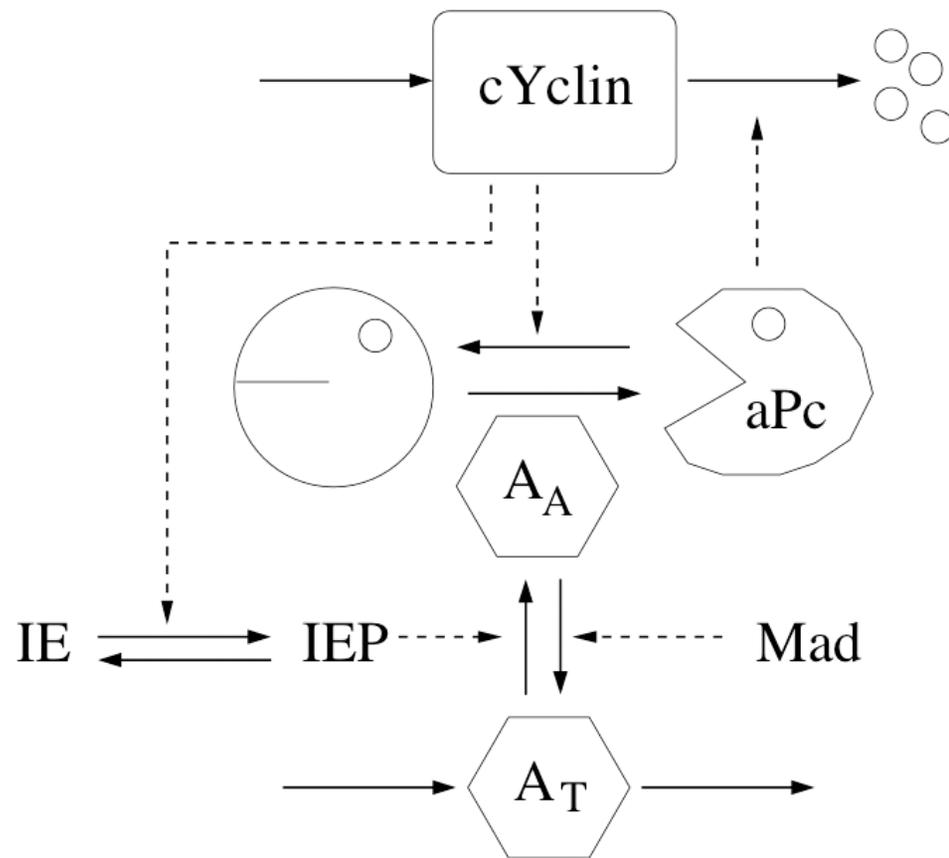
$$P' = \text{Factiv}(P) * (1 - P) - \text{Fdecay}(Y, P) * P$$

$$A' = k_5 p + k_5 p p * ((m * Y / J_5)^n) / (1 + (y * m / J_5)^n) - k_6 * A$$



Bifurc diagram for Y vs parameter m in full model
(with no QSS). This diagram is currently incomplete.

Fuller model

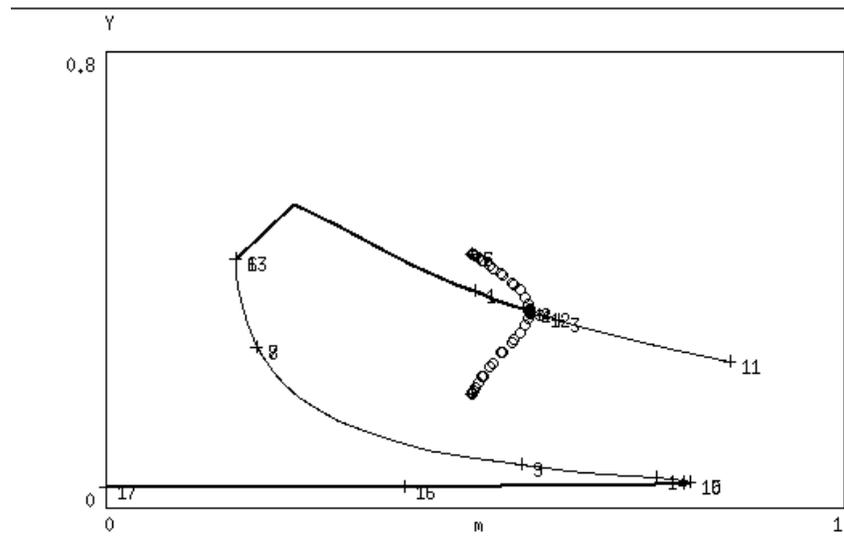


Fuller Basic Model

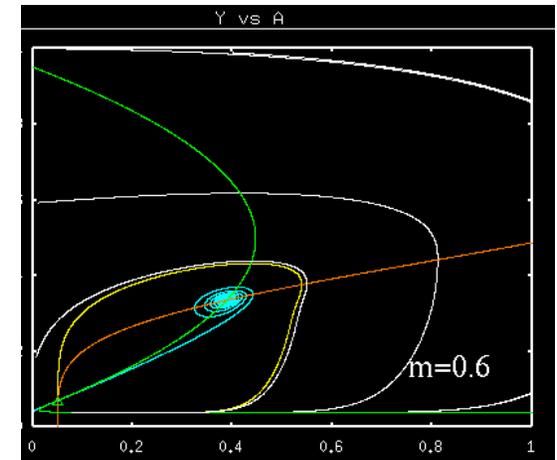
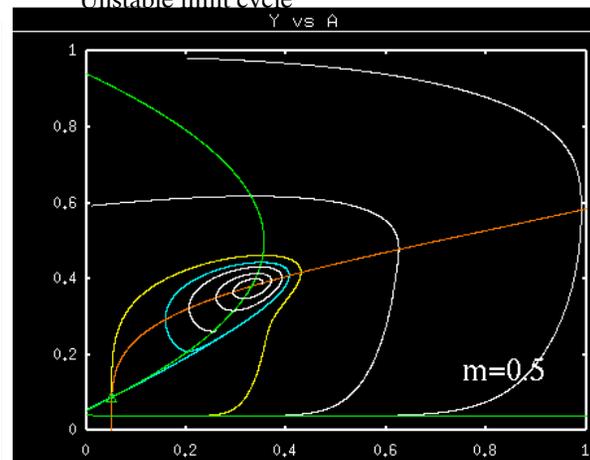
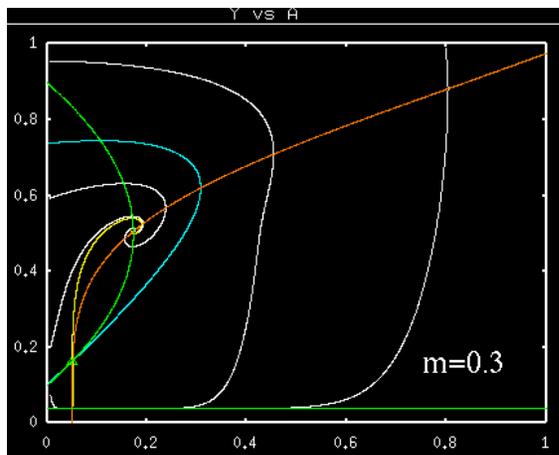
cYclin	$Y' = k_1 - (k_{2p} + k_{2pp}P)Y$
aPc (Cdh1)	$P' = F_{activ}(P, A_A)(1 - P) - F_{decay}(Y, P)P$
Cdc20T	$A'_T = k_{5p} + k_{5pp} \frac{(mY/J_5)^n}{1 + (Ym/J_5)^n} - k_6 A_T$
Cdc20A	$A'_A = k_7 I_P \frac{A_T - A_A}{J_7 + A_T - A_A} - k_6 A_A - k_8 [\text{Mad}] \frac{A_A}{J_8 + A_A}$
IEP	$I'_P = k_9 mY(1 - I_P) - k_{10} I_P$
Mass	$m' = \mu m \left(1 - \frac{m}{m_s}\right)$

$$F_{activ}(P, A_A) = \frac{k_{3p} + k_{3pp}A_A}{J_3 + 1 - P}$$

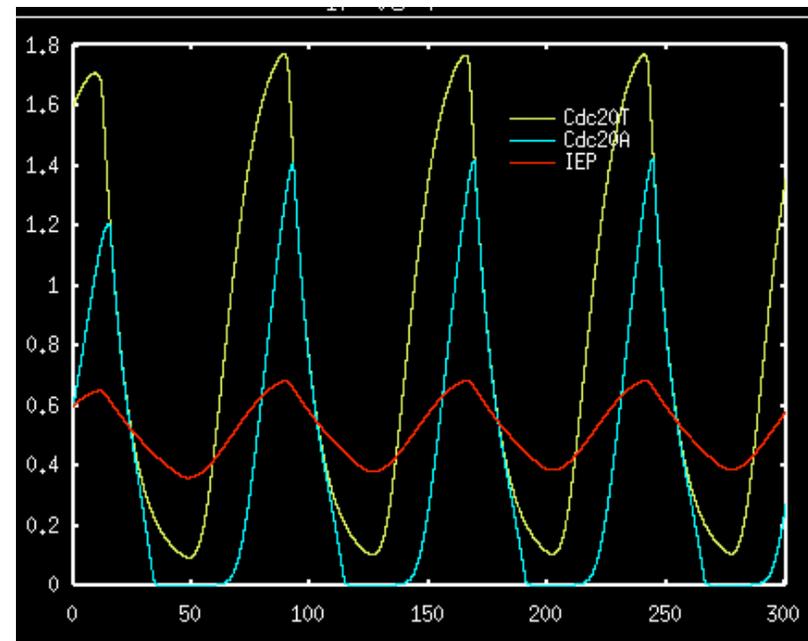
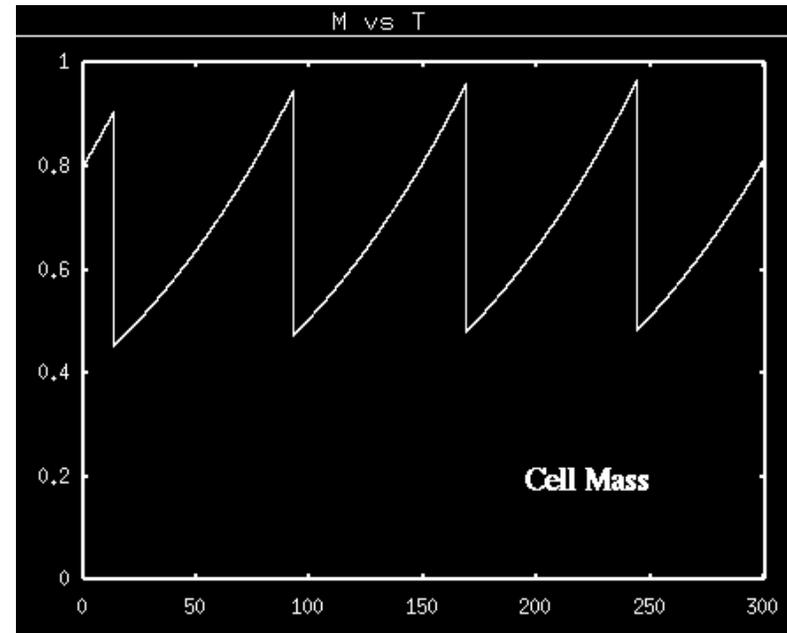
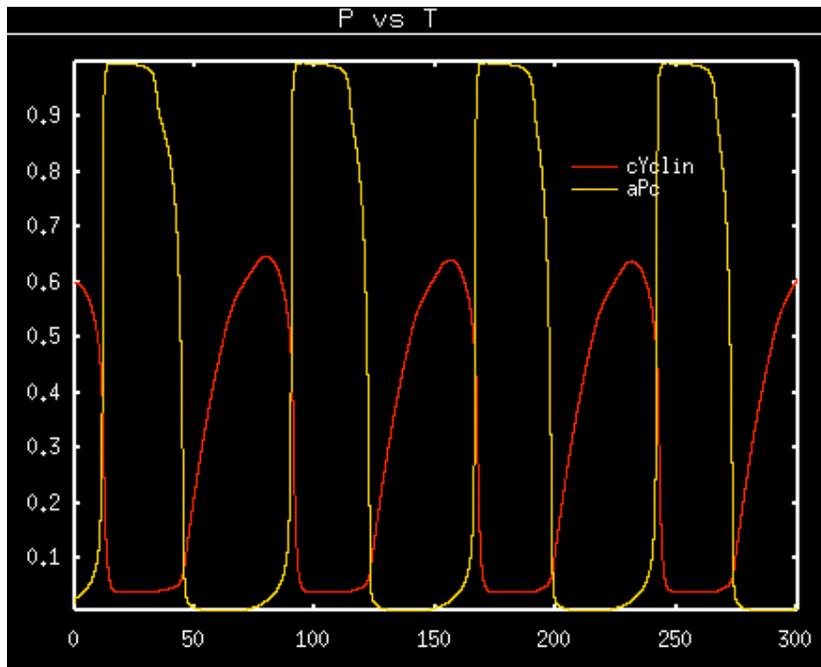
Part of the Bifurcation diagram



Unstable limit cycle



Full basic model



Accomplishments:

Understanding the complex regulatory system in a modular fashion, adding complexity gradually so as to see what each part of the network does. Identifying parameters using random search in parameter space. Accounting for many distinct mutants that are missing specific components, or have overexpression of other components. Assembling the bifurcation structure of the network as a whole.

Cell cycle components

In different cells, the chemicals have different names.. Making the field challenging.

Type of component	Fission yeast	Budding yeast	Frog egg	Mammalian cell
CDK (G2/M)	Cdc2	Cdc28	Cdk1,2	Cdk1,2
CDK (G1/S)	Cdc2	Cdc28	Cdk2 ^b	Cdk2,4
Cyclin (G2/M)	Cdc13	Clb1-4	Cyclin A,B	Cyclin A,B
Cyclin (G1/S)	Cig2	Clb5-6, Cln1-3	Cyclin E ^b	Cyclin D,E
Tyrosine kinase	Wee1, Mik1	Swel	Wee1	Wee1
Tyrosine phosphatase	Cdc25	Mih1	Cdc25C	Cdc25
CDK inhibitors ^c	p25 ^{Rum1}	p40 ^{Sic1} , p83 ^{Far1}	p27 ^{Xic1} , p28 ^{Kix1}	p16 ^{Ink4} , p21 ^{Cip1} , p27 ^{Kip1} , p57 ^{Kip2}
Transcription factors	Res1/Cdc10	Mbp1/Swi6	?	E2F
Licensing factors ^d	Cdc18 Mcm2-6	Cdc6 Mcm2-5, 7	Cdc6 Mcm2-5, 7	? Mcm2-5, 7

References

You can get other ODE files and references from Tyson's website <http://mpf.biol.vt.edu/Research.html>

Tyson, Chen & Novak (2001)
Nature Rev Molec Cell Biol **2**:908.

Tyson, Csikasz-Nagy & Novak (2002)
BioEssays **24**:1095.

Csikasz-Nagy et al. (2006)
Biophys. J. **90**:4361.