Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

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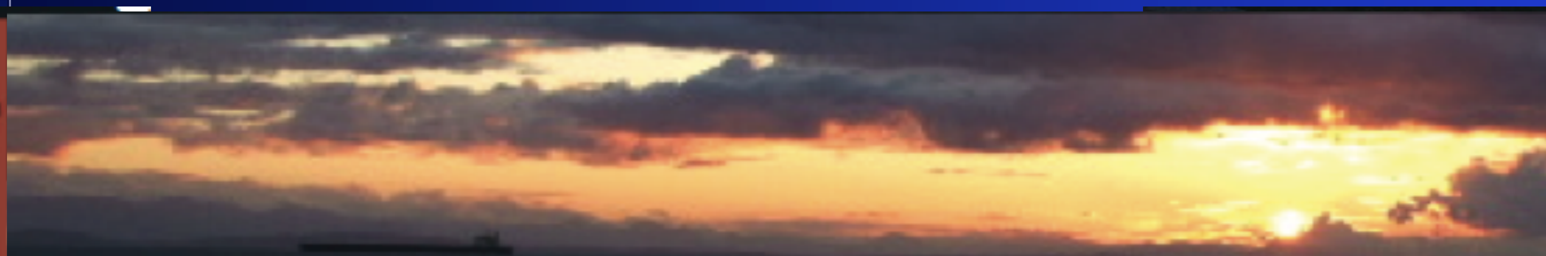
Biochemical motifs (5)



mprime

PIMS

www.math.ubc.ca/~keshet/MCB2012/

Basic GTPase signaling modules: other feedback and context

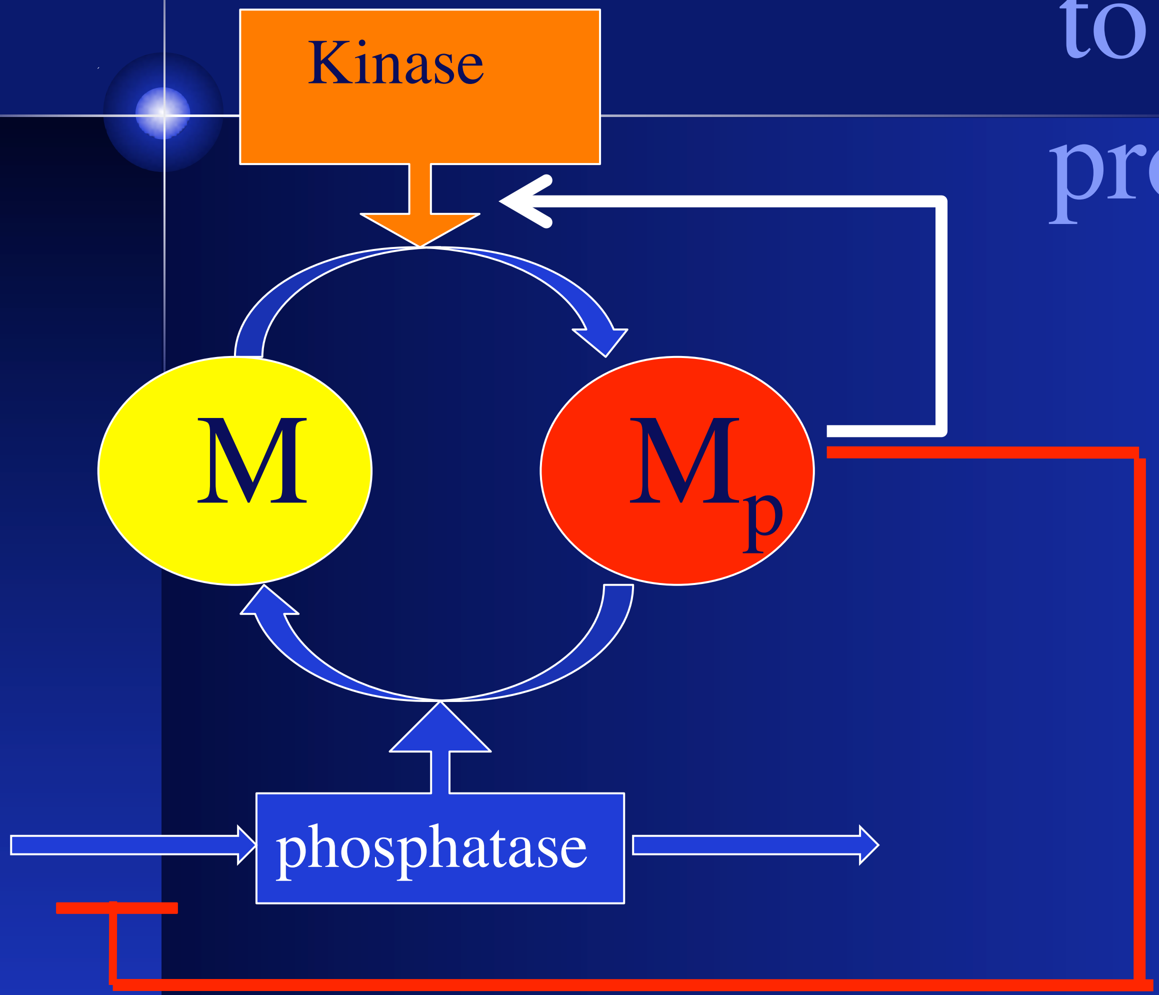
B.N. Kholodenko. Cell-signalling dynamics in time and space. Nature Reviews Molecular Cell Biology, 7(3):165–176, 2006

Other feedback

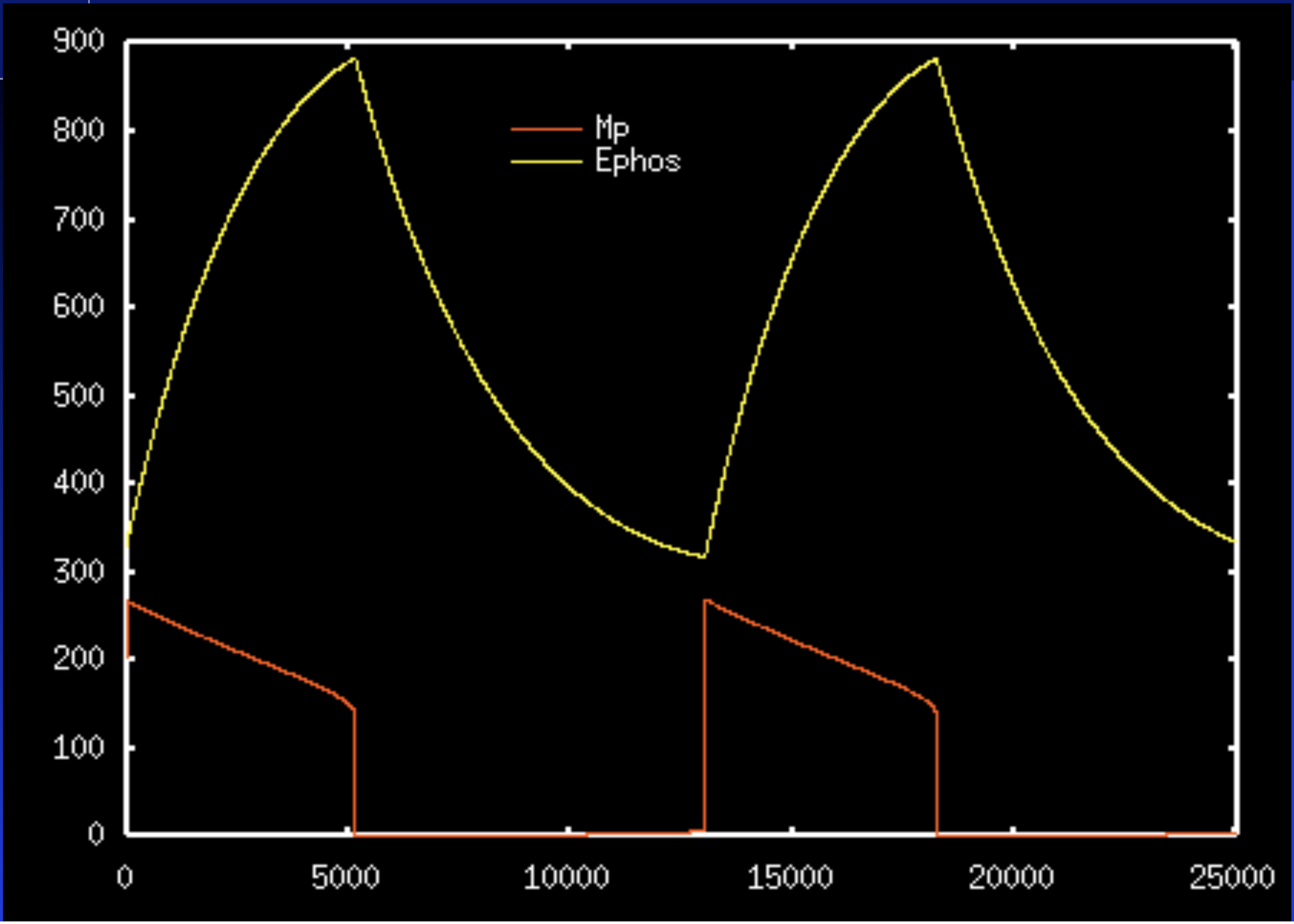
There are many other feedback effects possible.

Here is one more

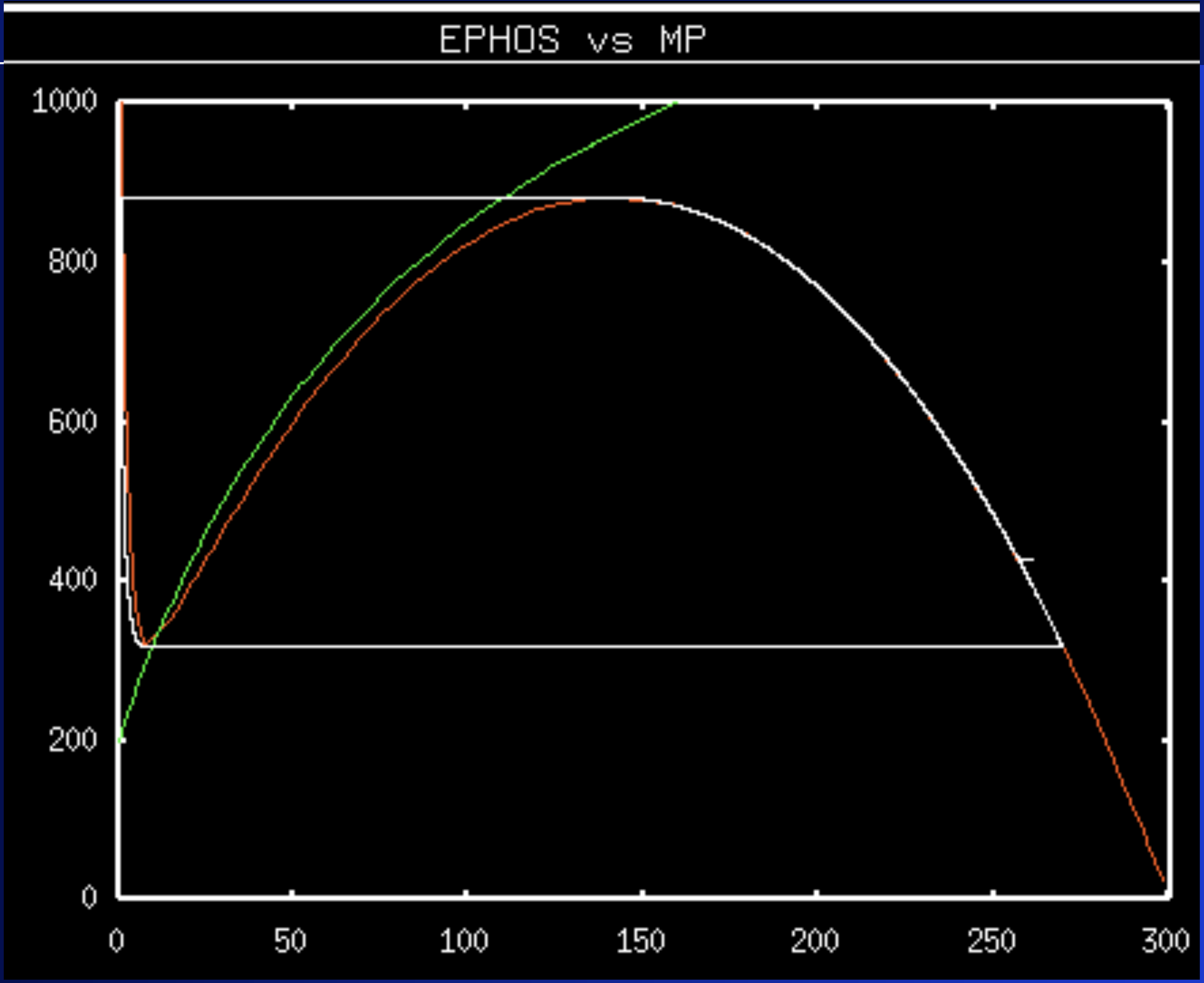
Positive feedback to phosphatase production rate



Time Behaviour of GTPase model



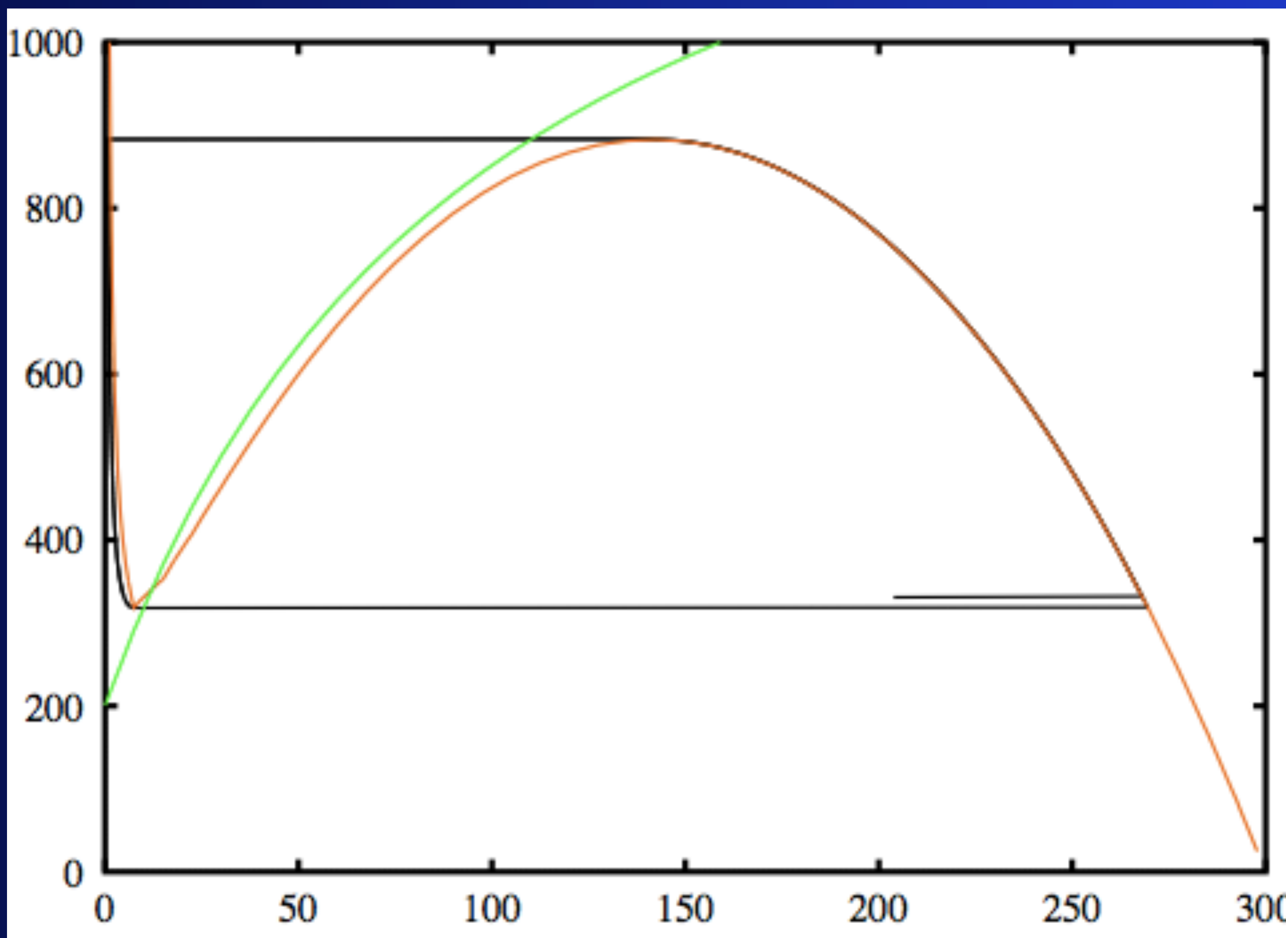
Stable limit cycle



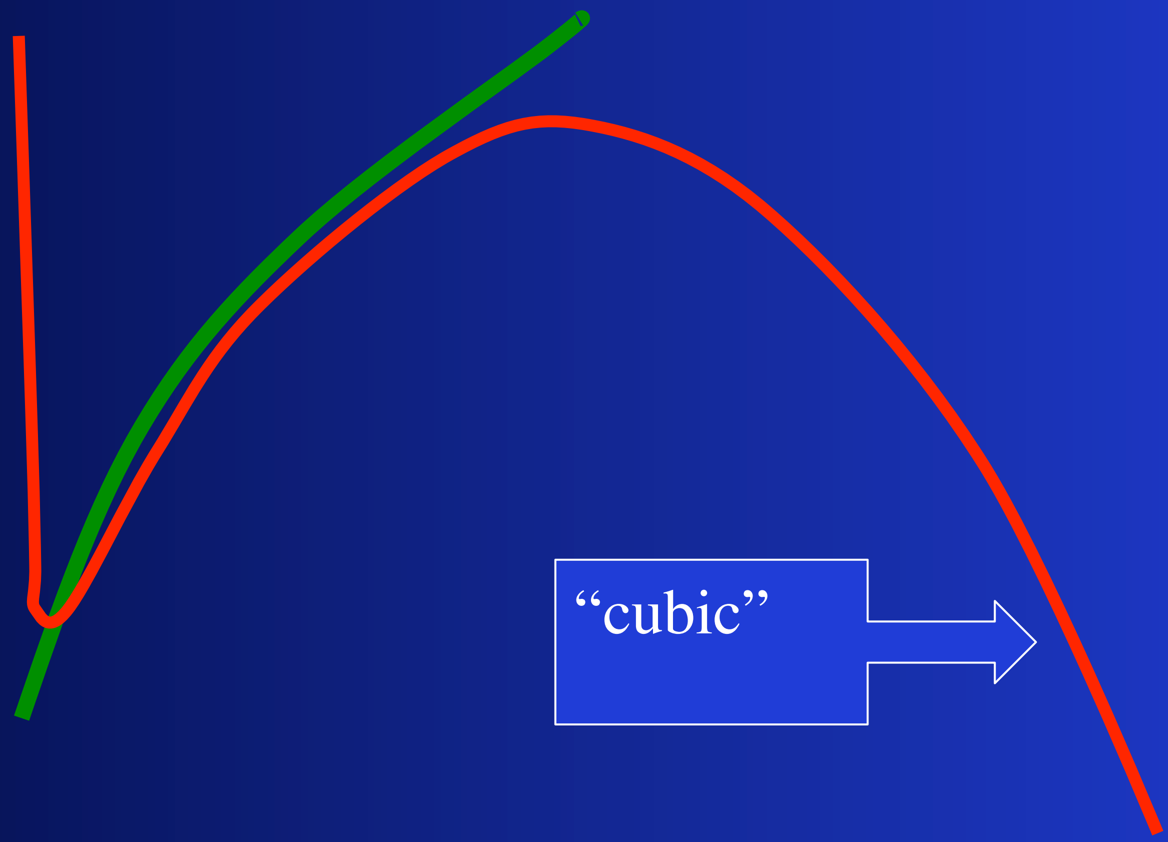
XPP file

```
# Kholod06Oscill_c.ode
#
# Kholodenko (2006) Nat Rev Mol Cell Bio 7, p 165
# Box 2 Example (c)
#
# M is protein and Mp is its phosphorylated form
# Ephos is the phosphatase

Mp'=vkin(Mp,Mtot-Mp)-vphos(Mp,Mtot-Mp)
Ephos'=v_phossyn(Mp)-v_phosdeg(Ephos)

vkin(Mp,M)=((k_kincat*Ekin*M)/(Km1+M))*((1+A*(Mp/Ka))/(1+(Mp/Ka)))
vphos(Mp,M)=k_phoscat*Ephos*Mp/(Km2+Mp)

v_phossyn(Mp)=V_phos0*(1+Ap*(Mp/Kd))/(1+(Mp/Kd))
v_phosdeg(Ephos)=k_phosdeg*Ephos

# these params have units that include per sec already
par k_kincat=1,A=100,Ka=500,Km1=500,Ekin=150
par k_phoscat=1,Km2=10
par Mtot=300

#Convert Kholodenko's params to per sec
# par V_phos0=200nm/hr, k_phosdeg=1/hr now in per sec:
par V_phos0=0.0555,Kd=100,Ap=7.5,k_phosdeg=0.000277

init Mp=300,Ephos=100

@ dt=0.01,total=50000,nout=500,xp=Mp,yp=Ephos,xlo=0,xhi=300,ylo=0,yhi=1000,bounds=10000
done
```

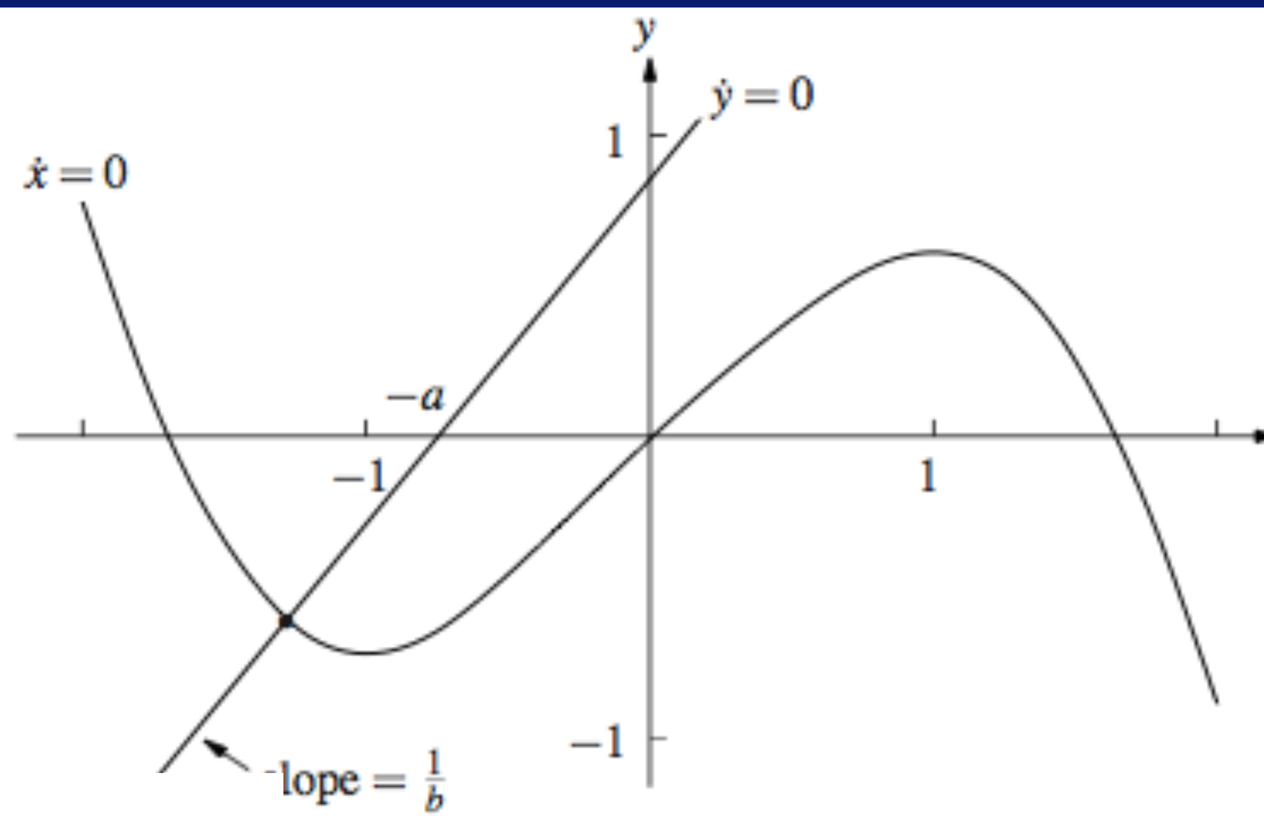
Stable limit cycle



Nullclines



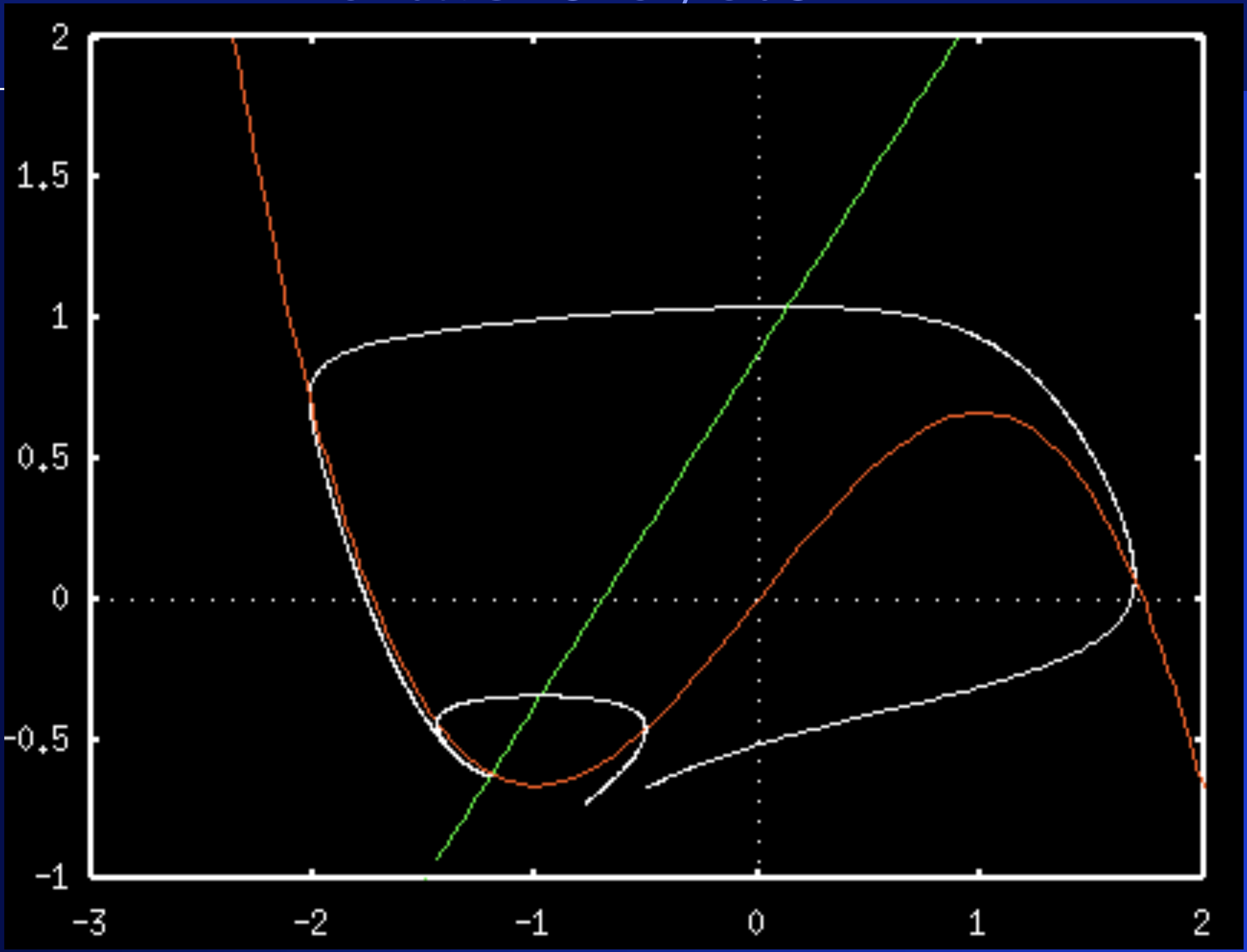
Classic FitzHugh Model



$$\frac{dx}{dt} = c\left[x - \frac{1}{3}x^3 - y + j\right],$$

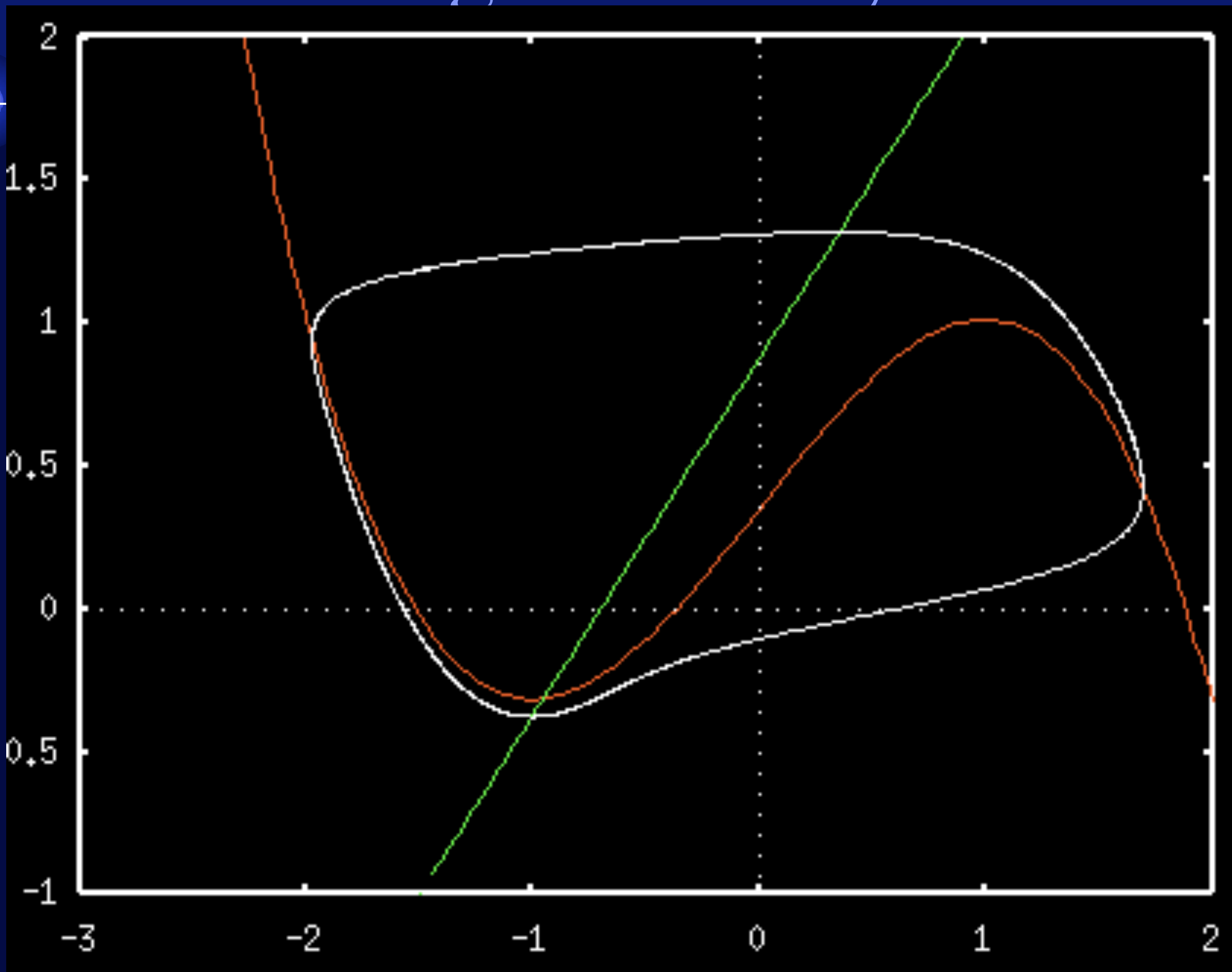
$$\frac{dy}{dt} = \frac{1}{c}[x + a - by]\,.$$

“Excitable system”



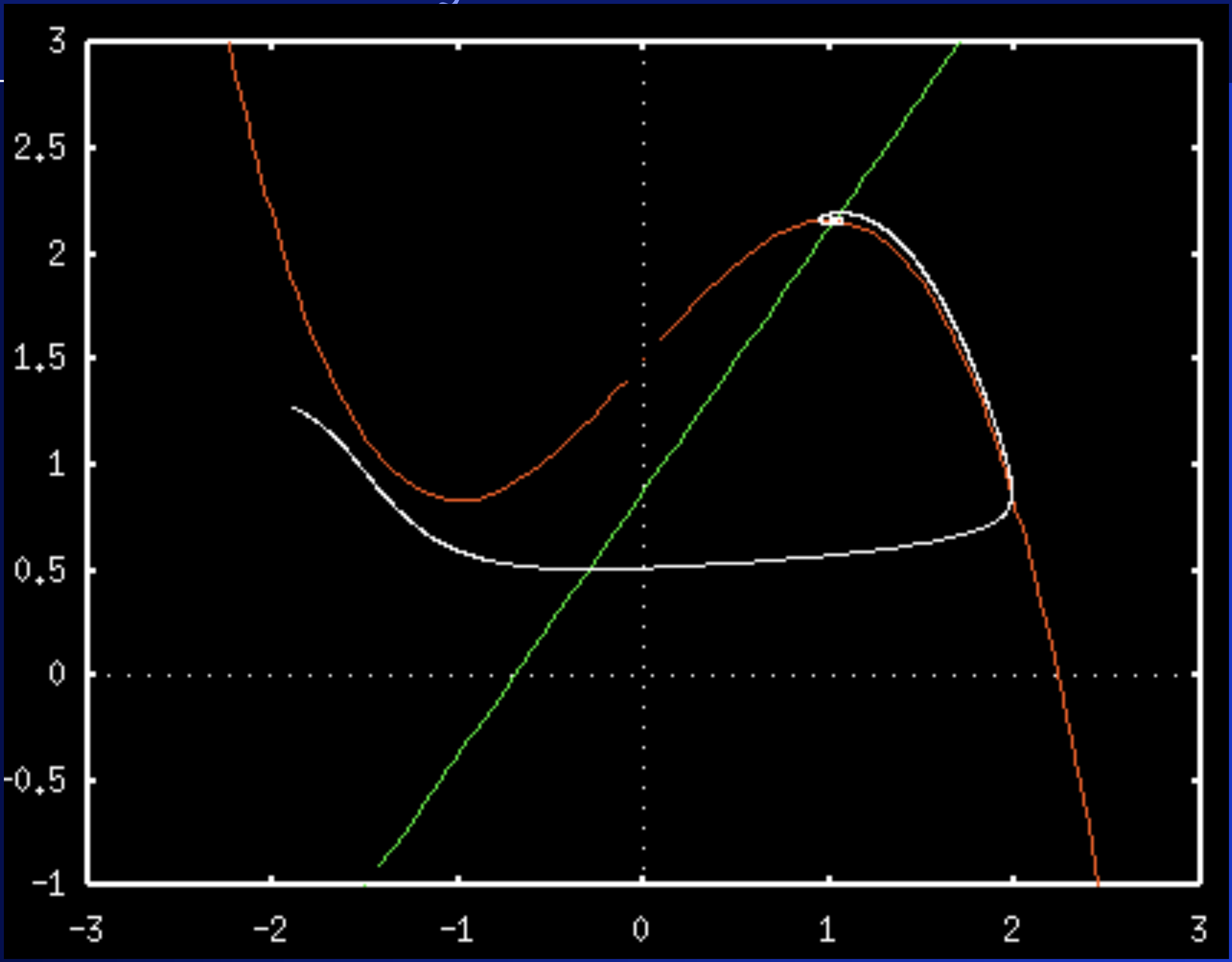
a=0.7, b=0.8, c=3, j=0

FitzHugh Limit cycle



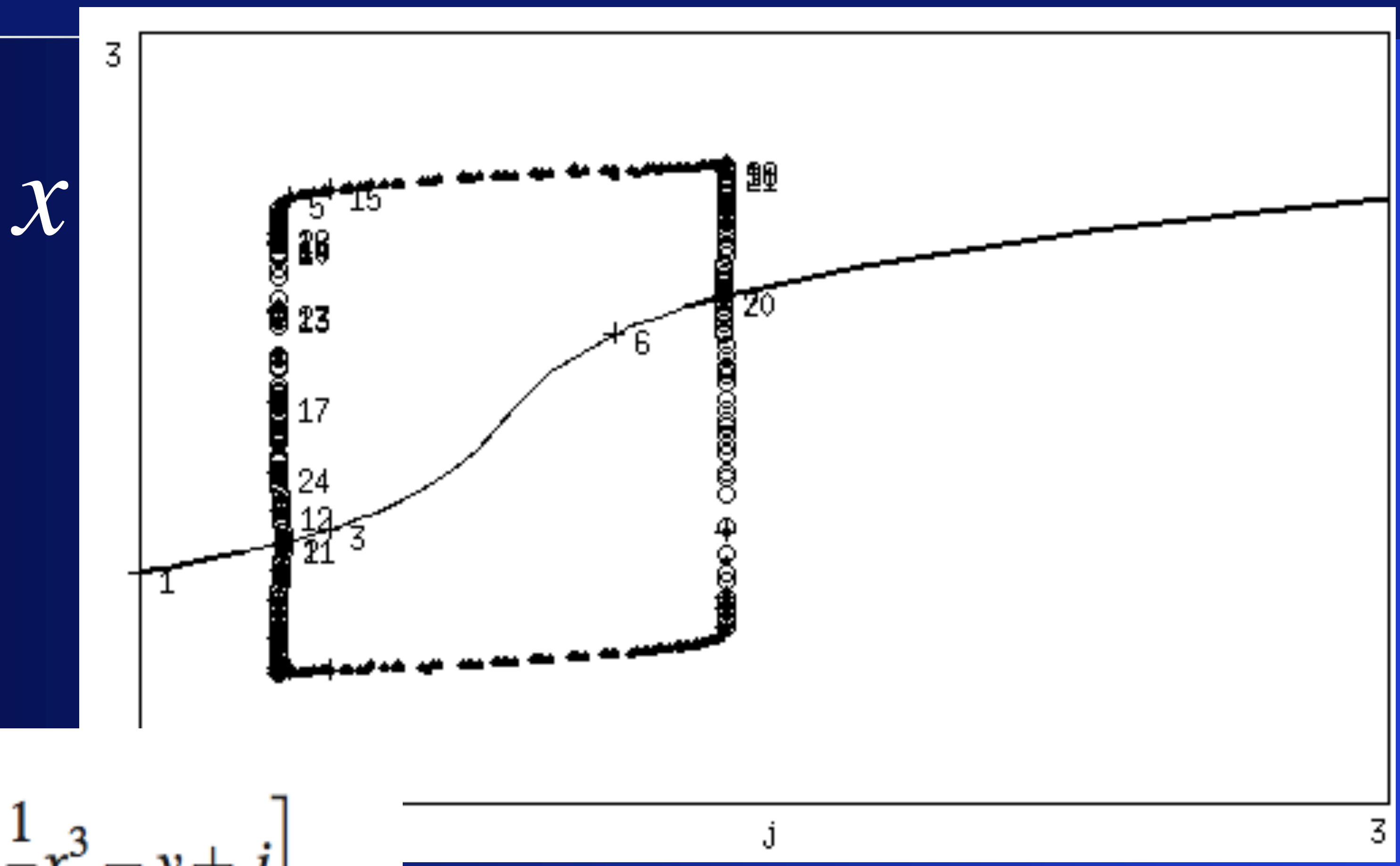
a=0.7, b=0.8, c=3, j=0.35

Limit cycle vanishes



a=0.7, b=0.8, c=3, j=1.5

Fitzhugh Bifurcation diagram



$$\frac{dx}{dt} = c\left[x - \frac{1}{3}x^3 - y + j\right],$$

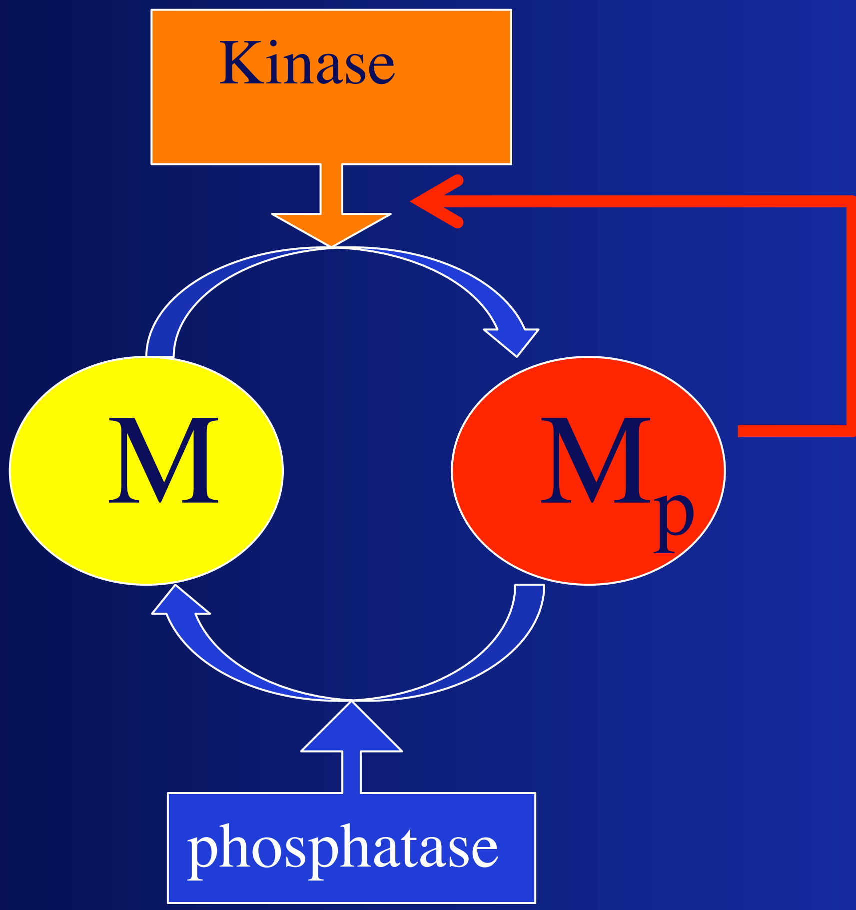
$$\frac{dy}{dt} = \frac{1}{c}[x + a - by]\,.$$

Conclusions

- The basic GTPase cycle can become a bistable switch in 2 ways

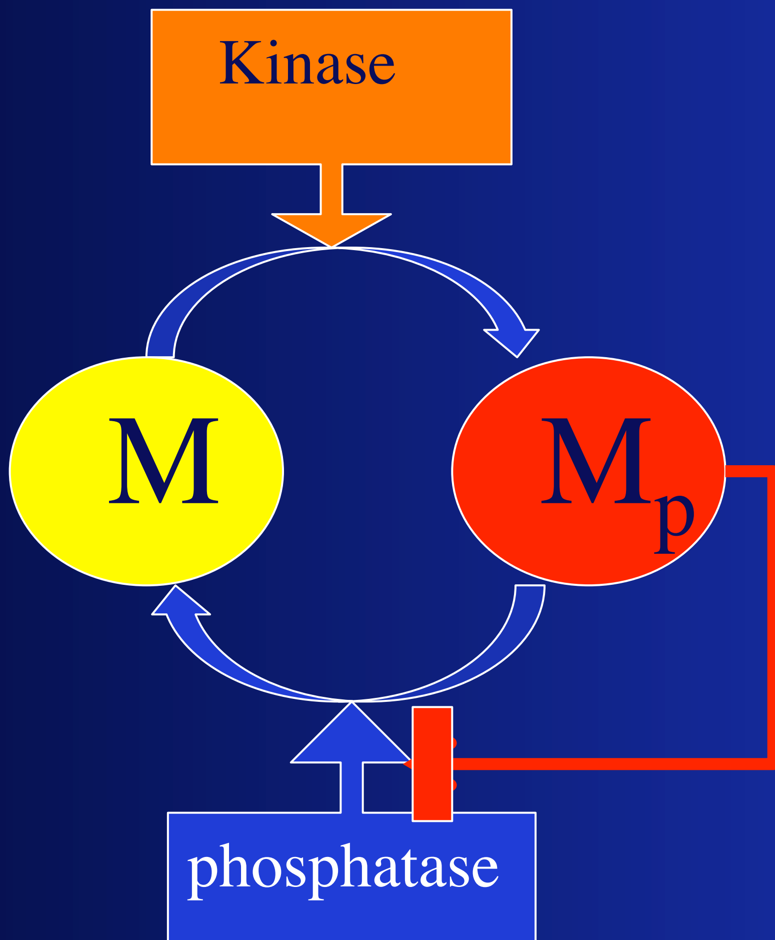
Ways of producing bistable switch

(1)



Ways of producing bistable switch

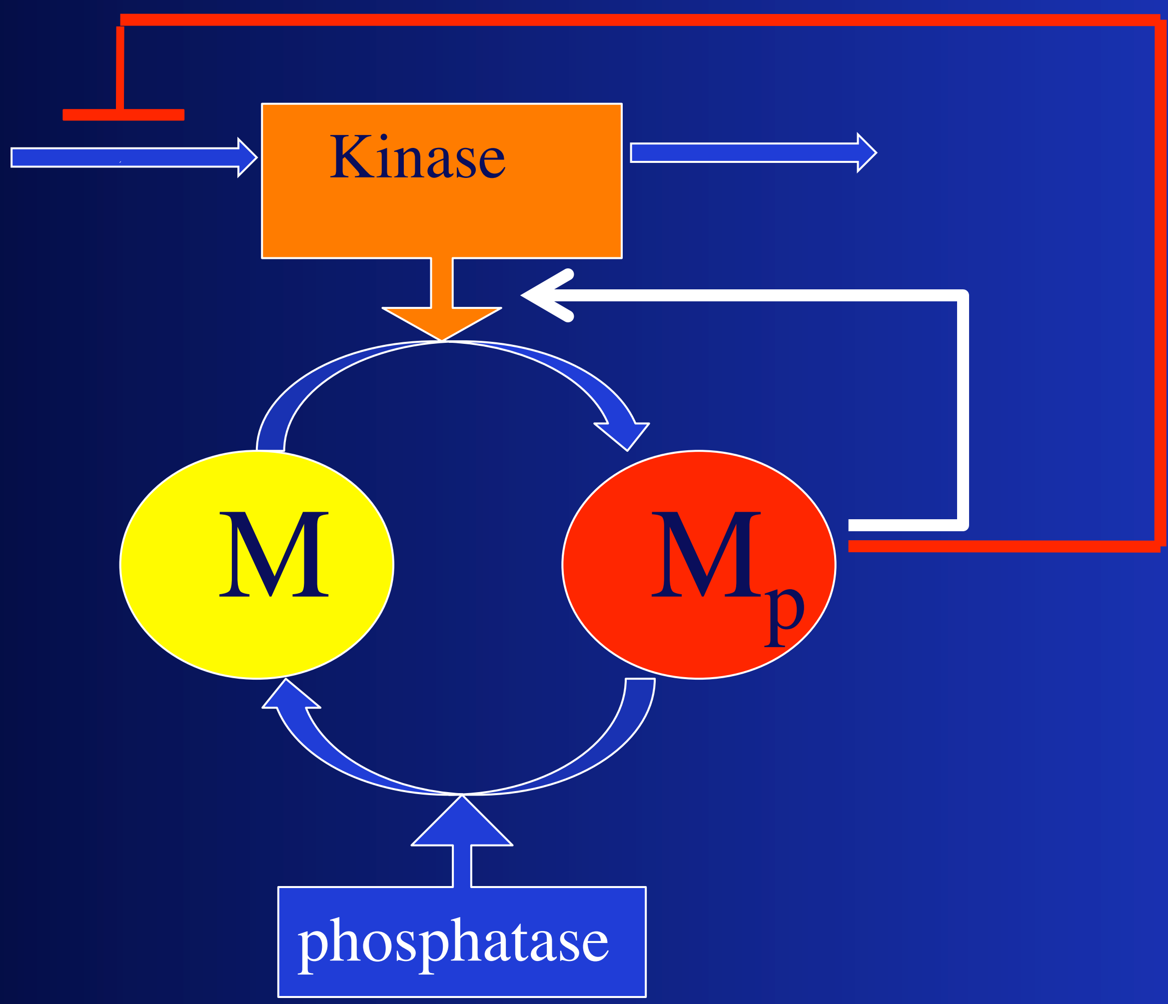
(2)



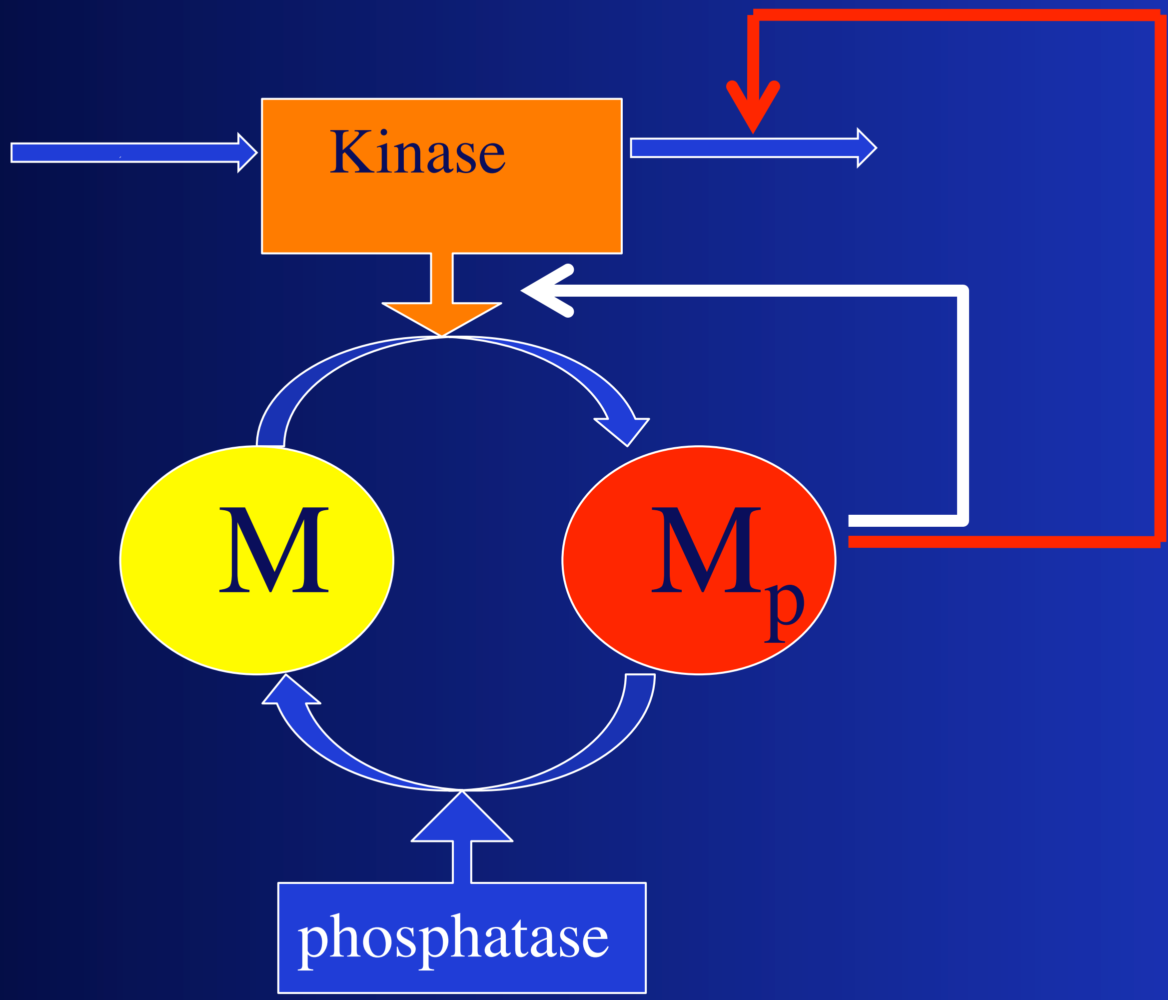
An additional feedback can lead to relaxation oscillations

- There are eight ways of achieving such behaviour

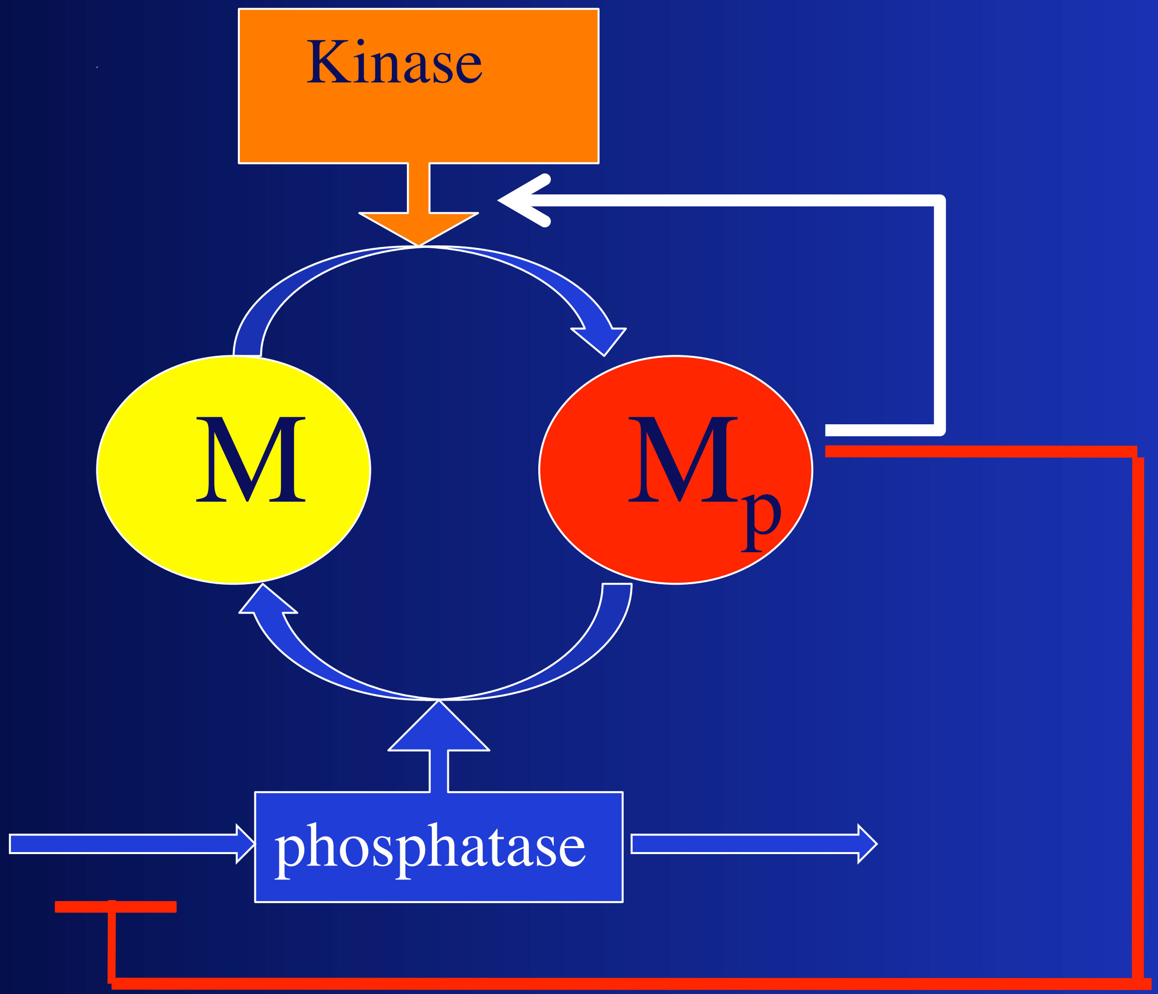
Feedback to kinase (1)



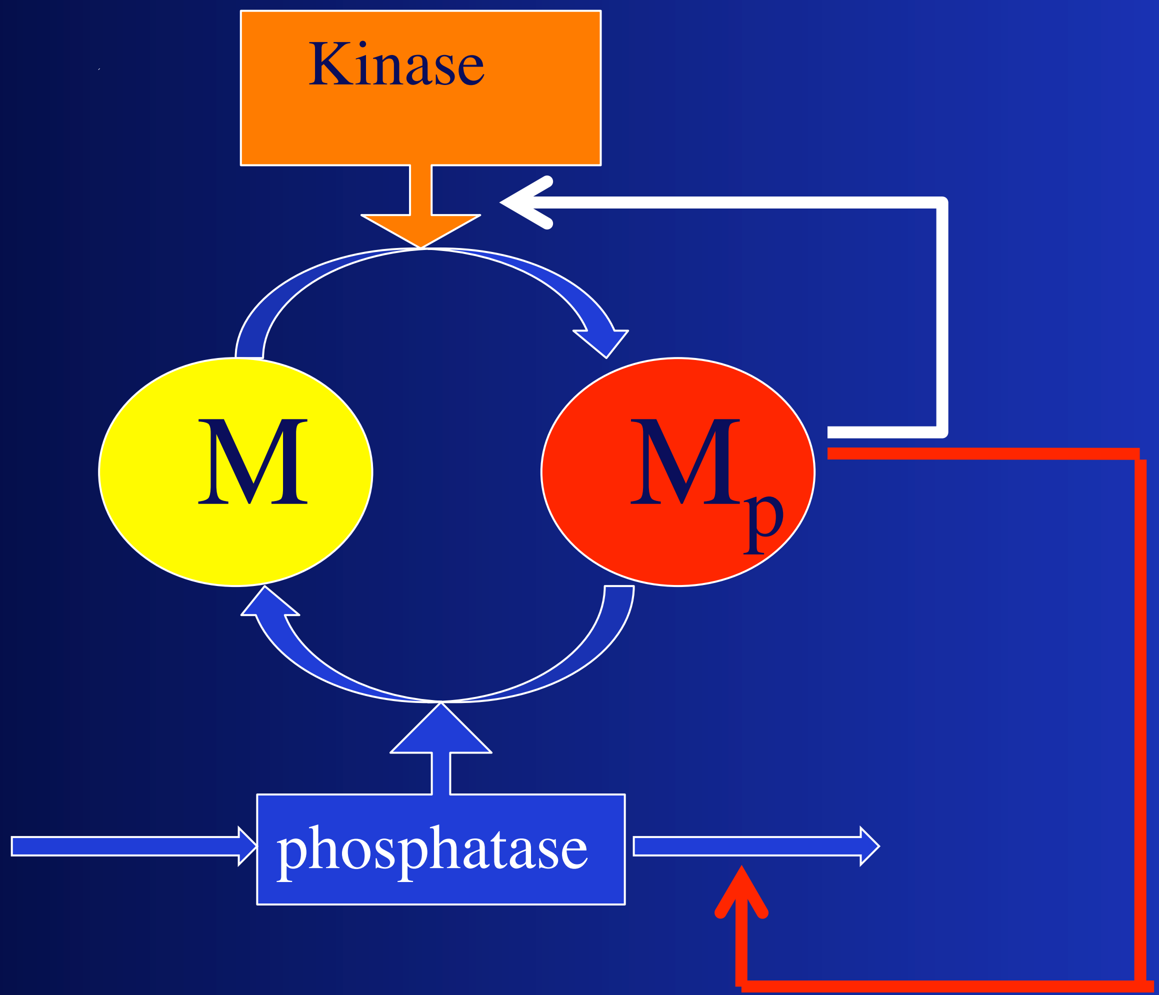
Feedback to kinase (2)

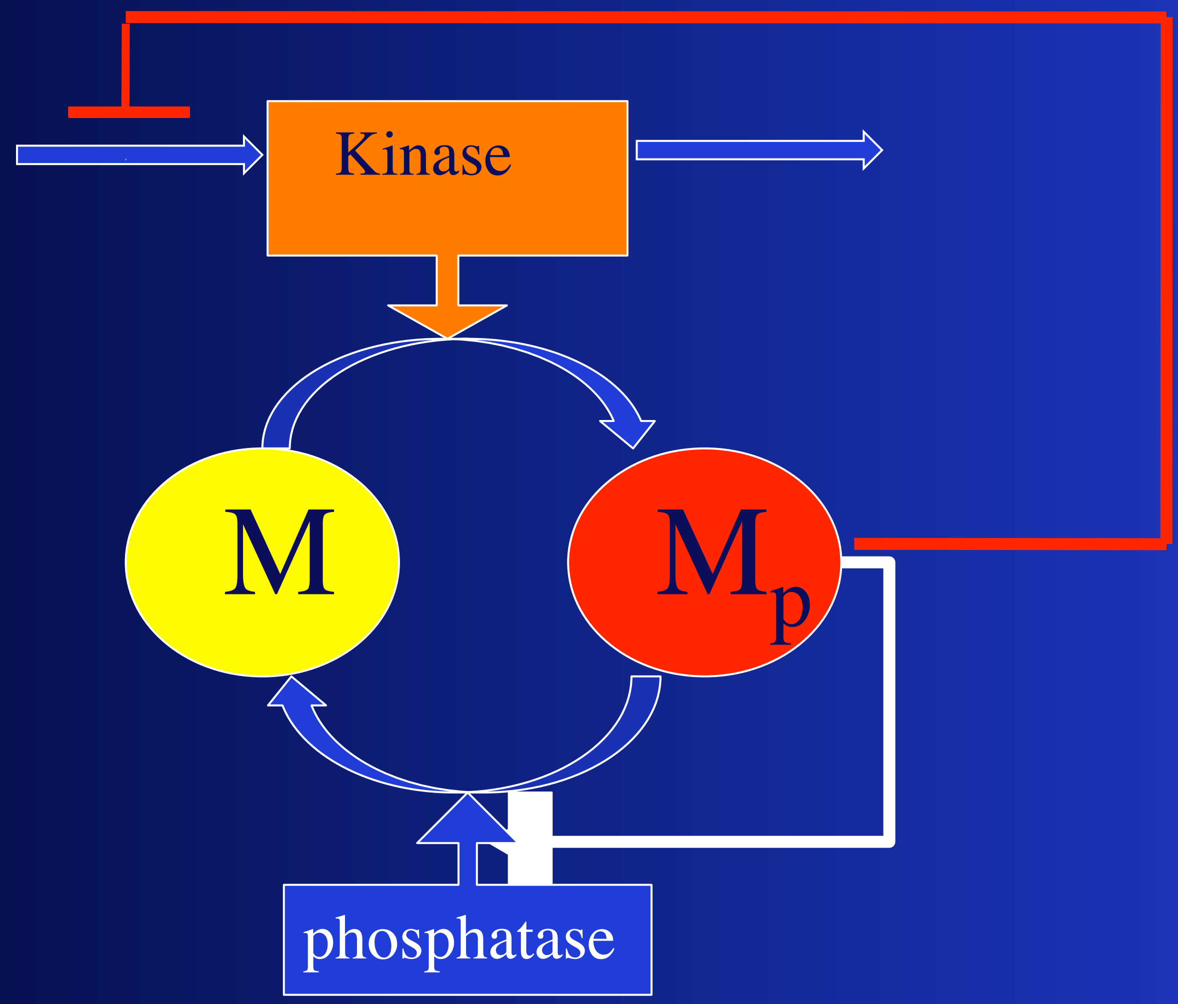


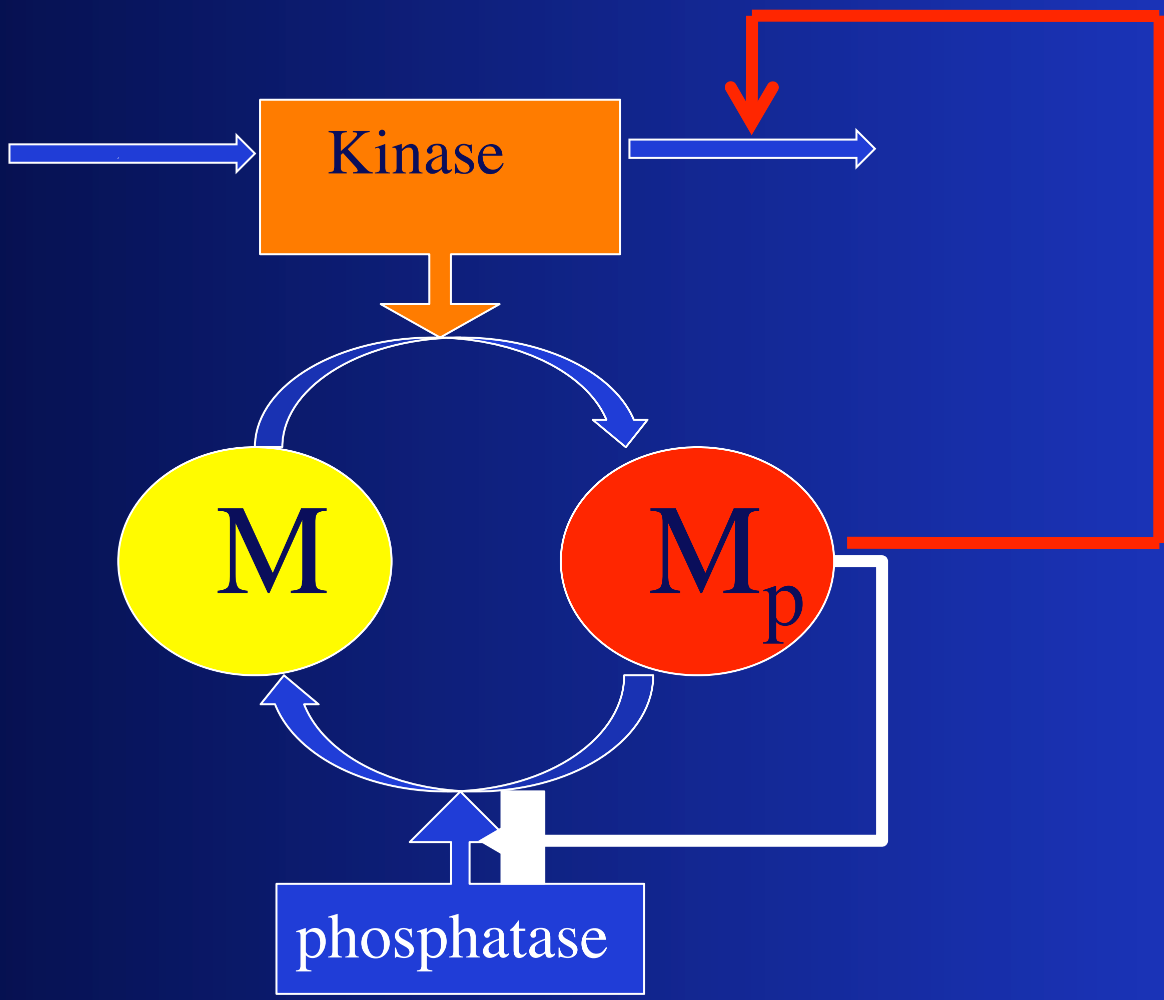
Feedback to phosphatase (1)

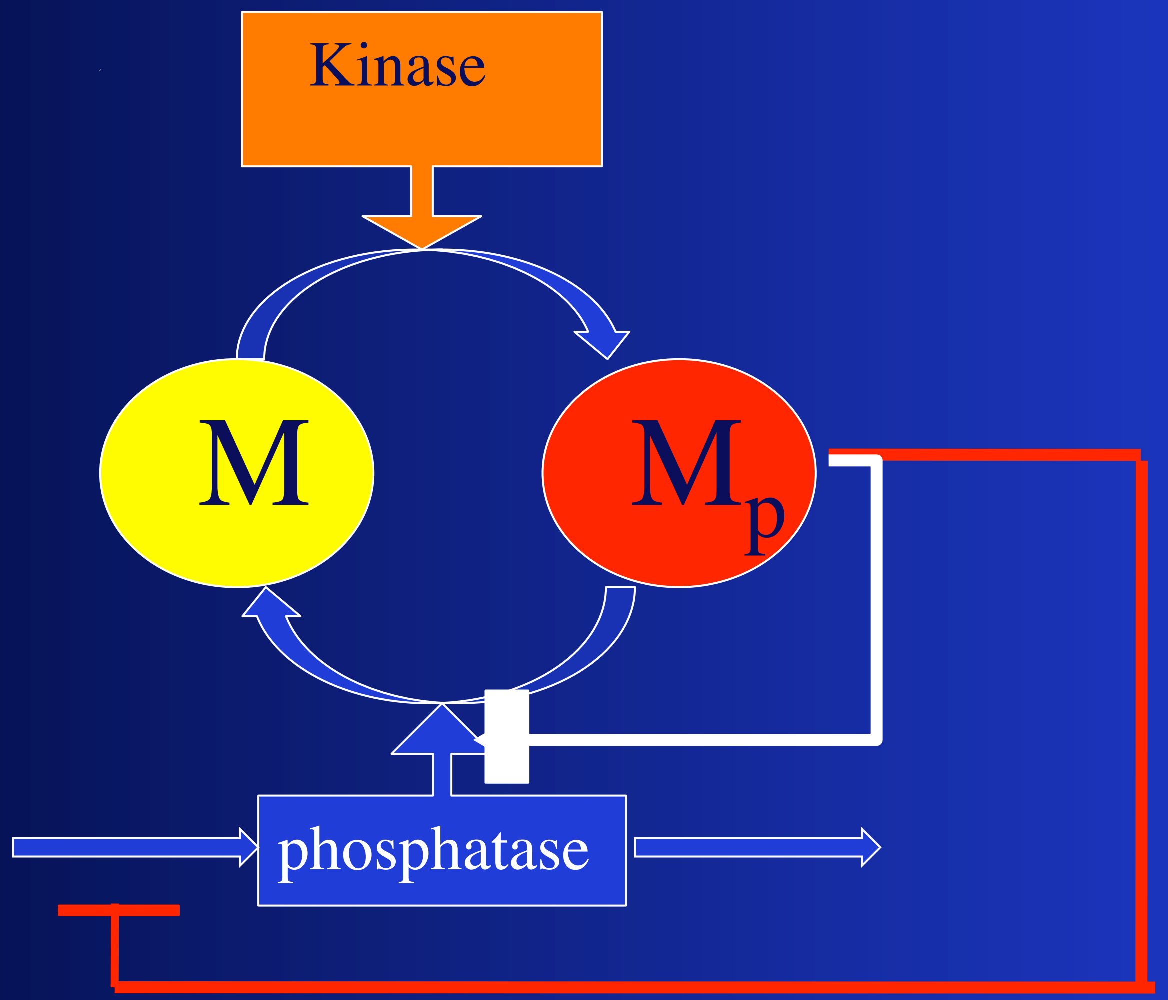


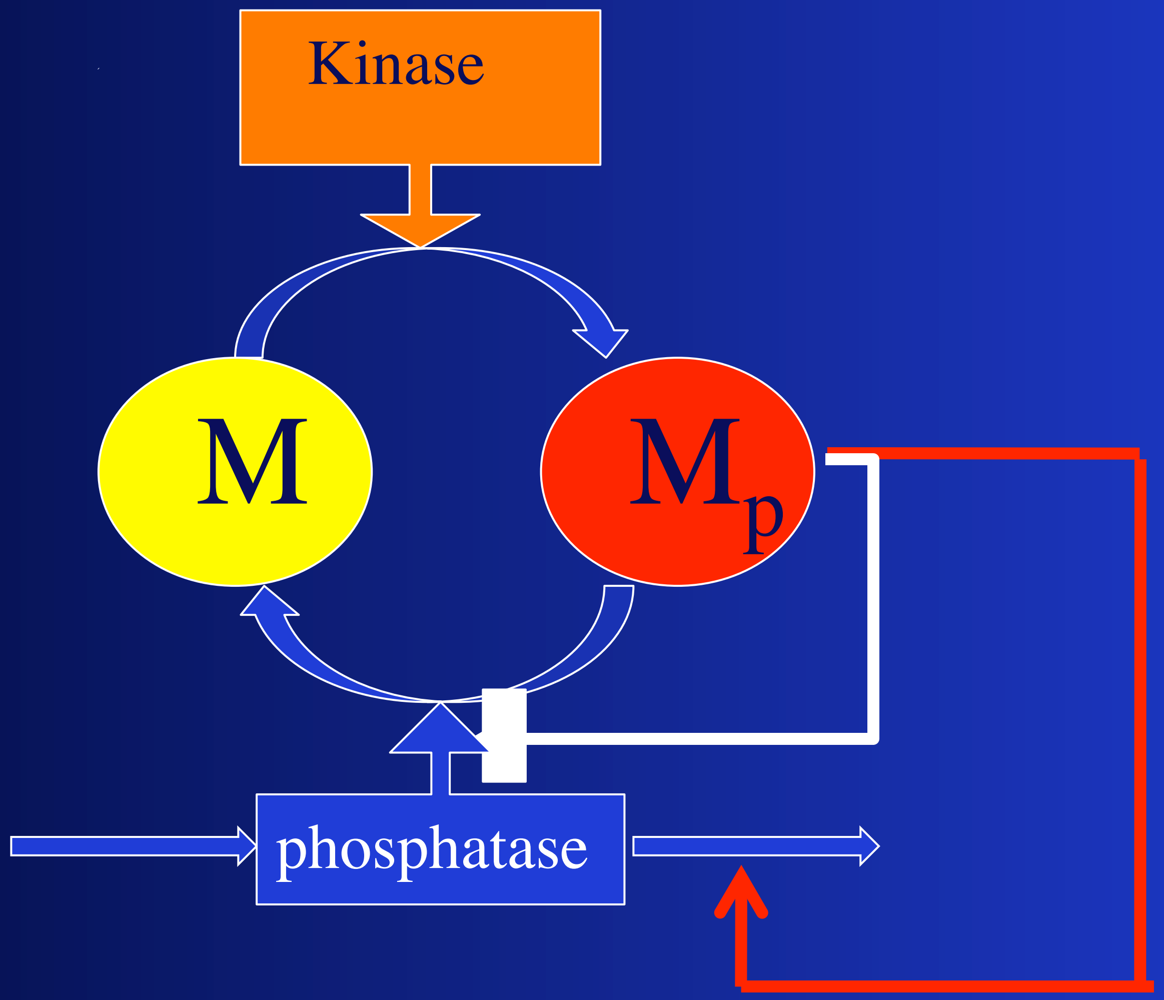
Feedback to phosphatase (2)




Kinase
M
M_p
phosphatase


Kinase
M
M_p
phosphatase


Kinase
M
Mp
phosphatase


Kinase
M
M_p
phosphatase

Further comments

Distinct GTPases can also interact with one another in pairs, trios, etc, producing larger circuits of positive and negative feedback networks.

See:
M.A. Tsyganov, W. Kolch, and B.N. Kholodenko. The topology design principles that determine the spatiotemporal dynamics of G-protein cascades. Mol. BioSyst., 8(3):730–743, 2012.