Mathematical Cell Biology Graduate Summer Course
University of British Columbia, May 1-31, 2012

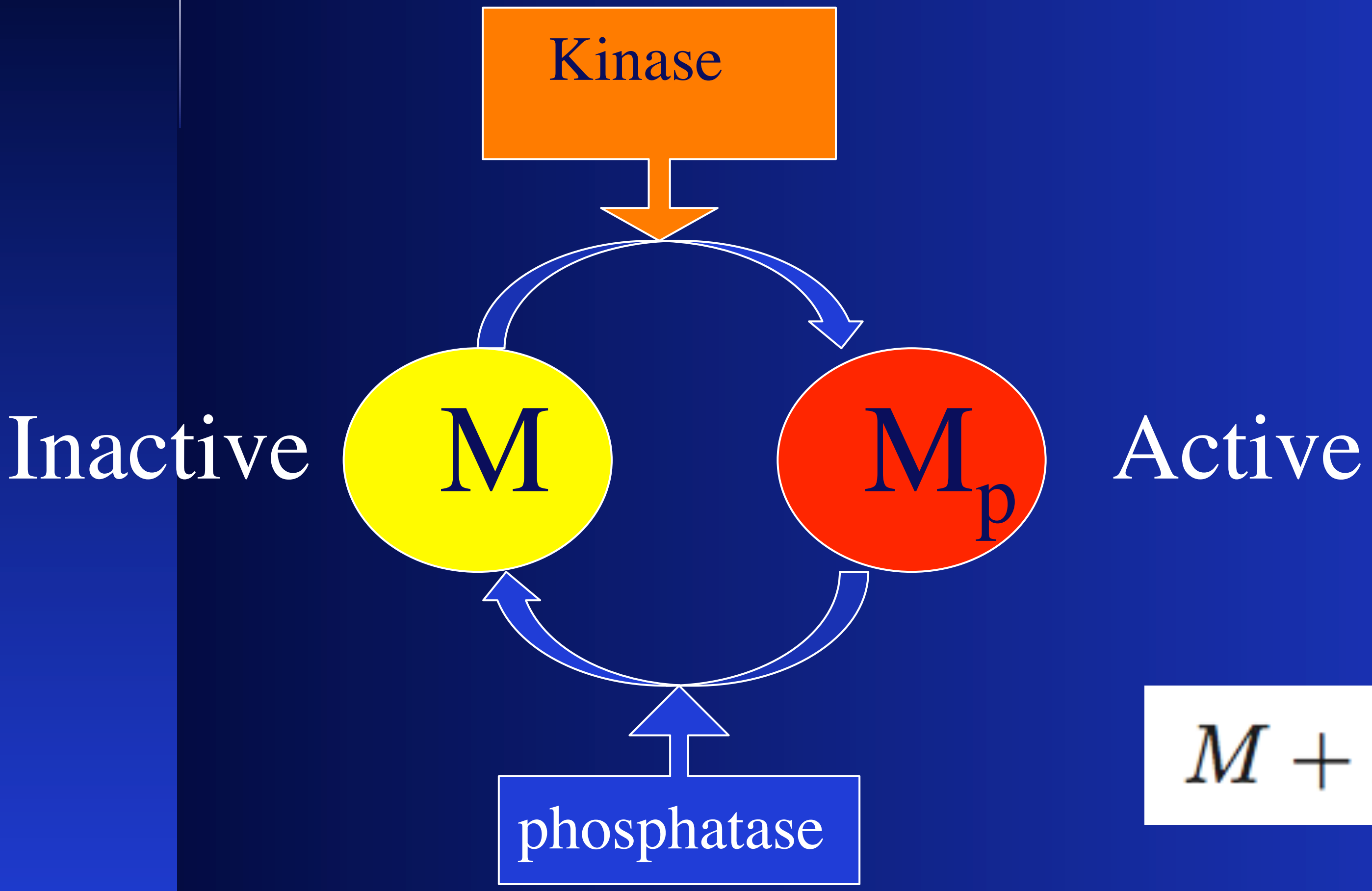
Leah Edelstein-Keshet

Biochemical motifs (4)

Basic GTPase signaling modules and feedback

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

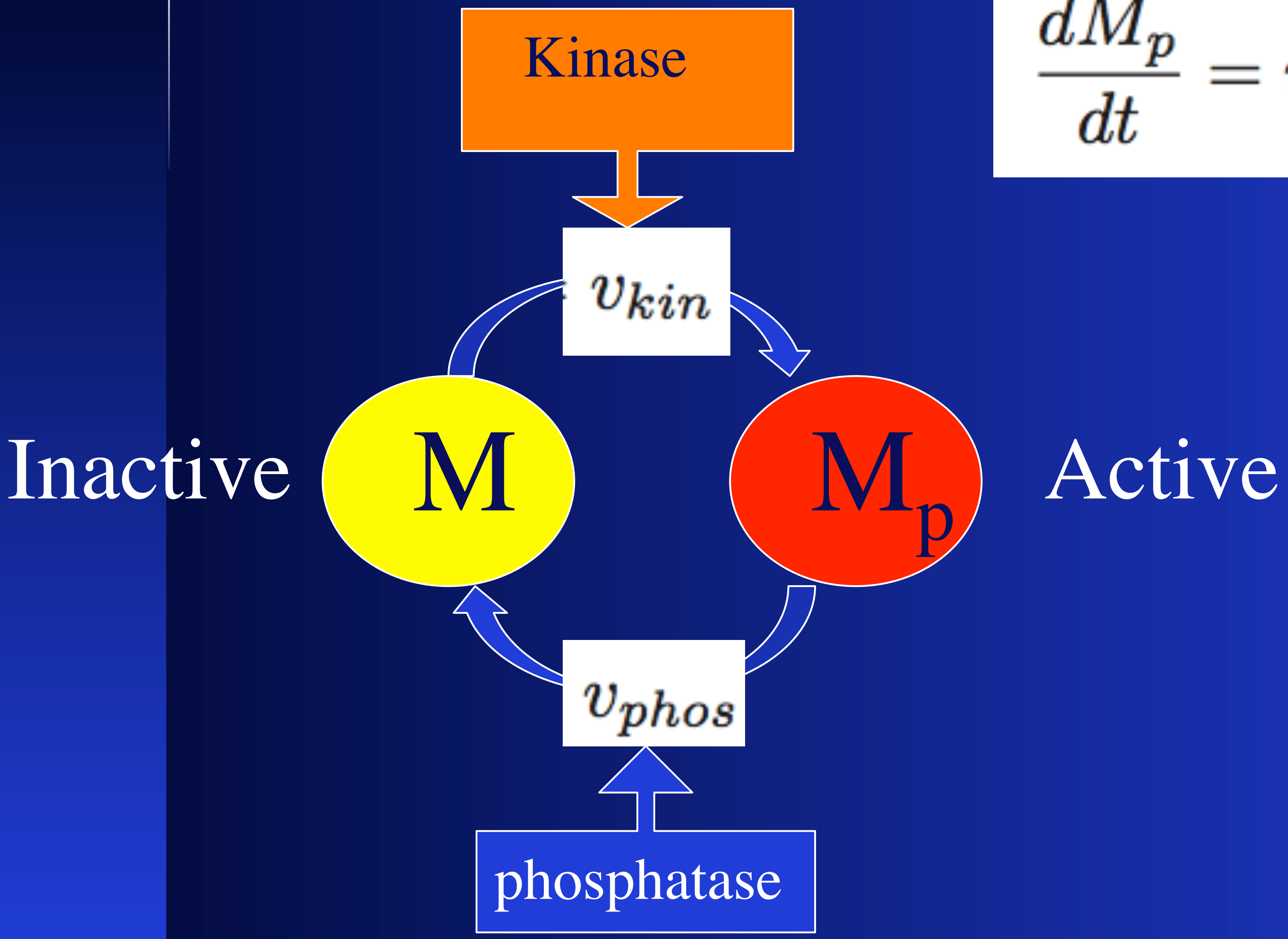
Phosphorylation cycle



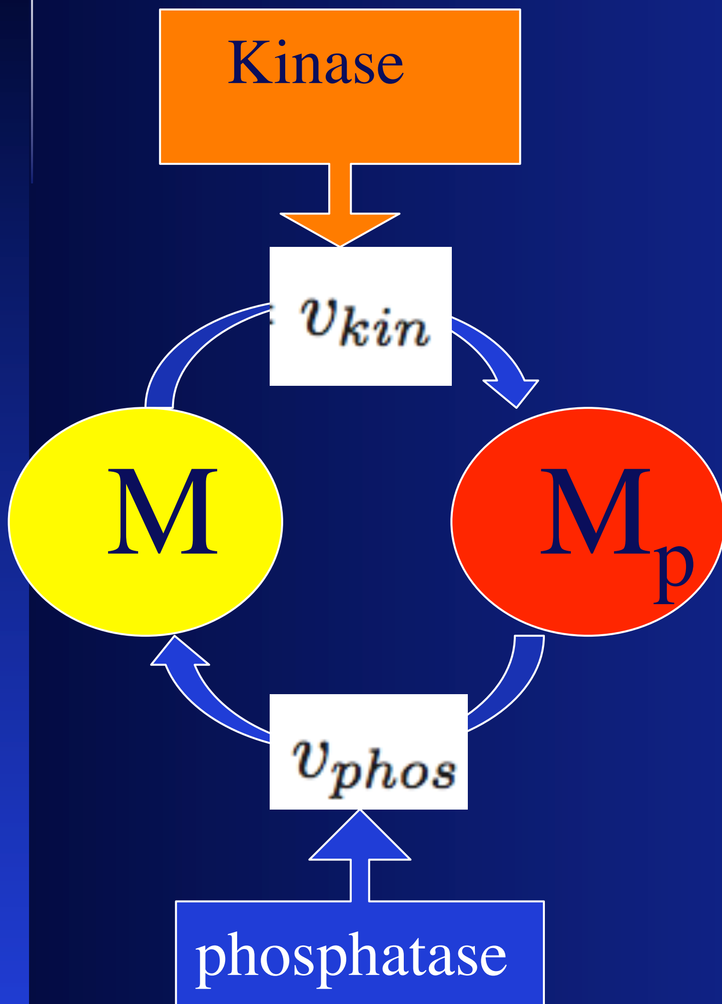
$$M + M_p = M_{tot}$$

Phosphorylation cycle

$$\frac{dM_p}{dt} = v_{kin} - v_{phos}$$



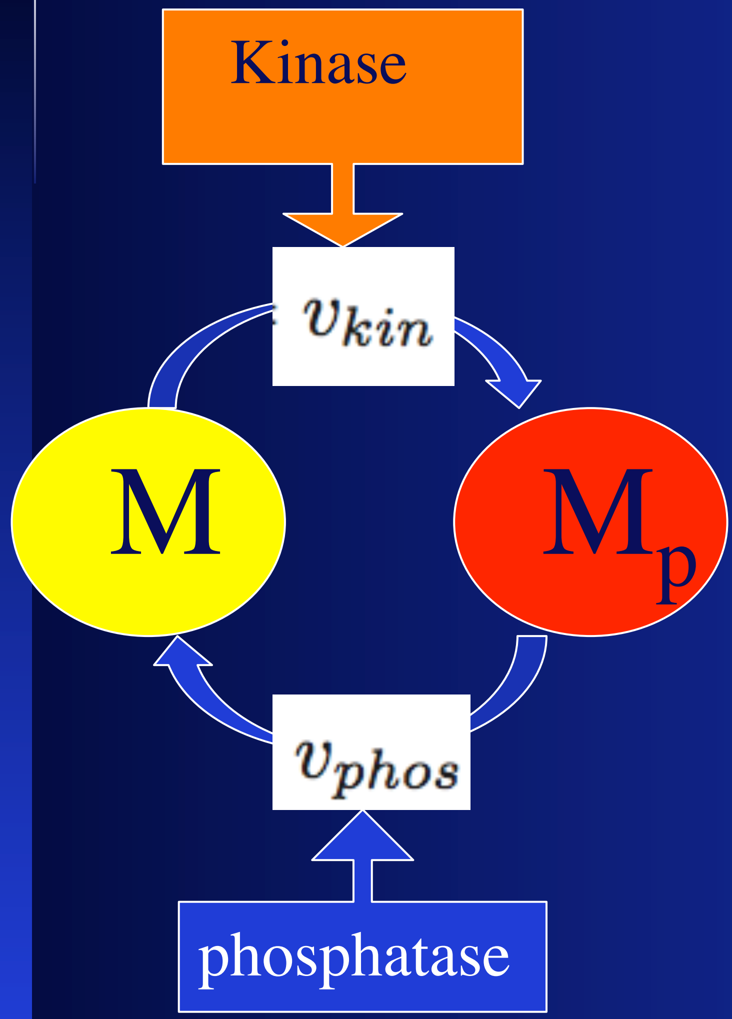
Each reaction is Michaelian



$$v_{kin} = \frac{V_1 M}{(K_{m1} + M)}$$

$$v_{phos} = \frac{V_2 M_p}{(K_{m2} + M_p)}$$

But we will allow the amt of kinase and phosphatase to vary too…

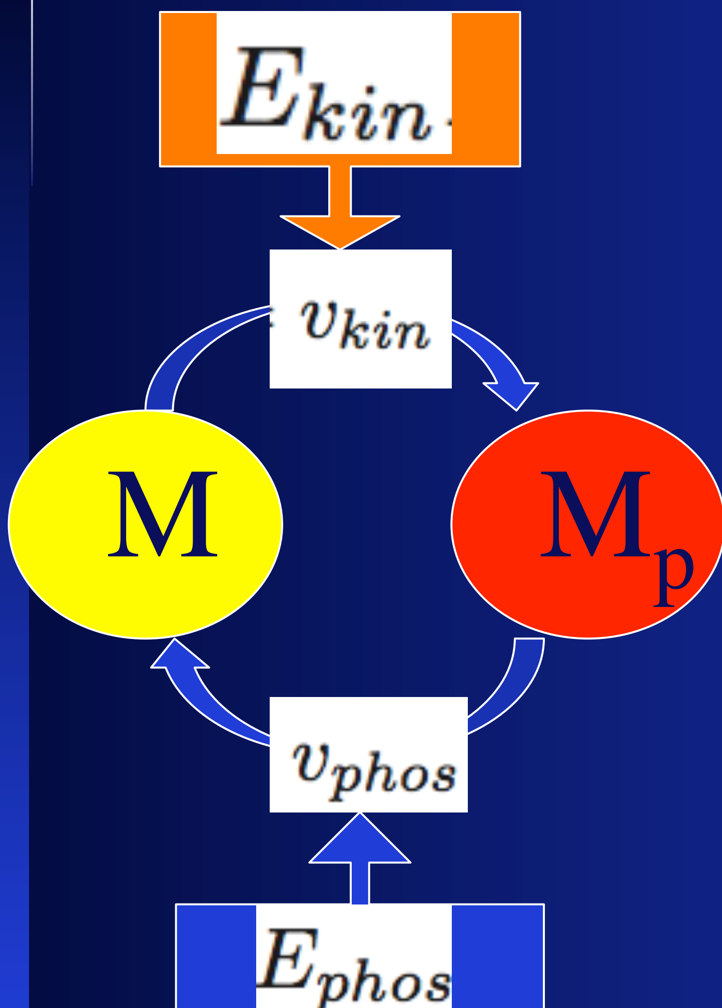


$$v_{kin} = \frac{V_1 M}{(K_{m1} + M)}$$

So we will express these rates in terms of total amounts of Kinase and Phosphatase

$$v_{phos} = \frac{V_2 M_p}{(K_{m2} + M_p)}$$

Full Expressions

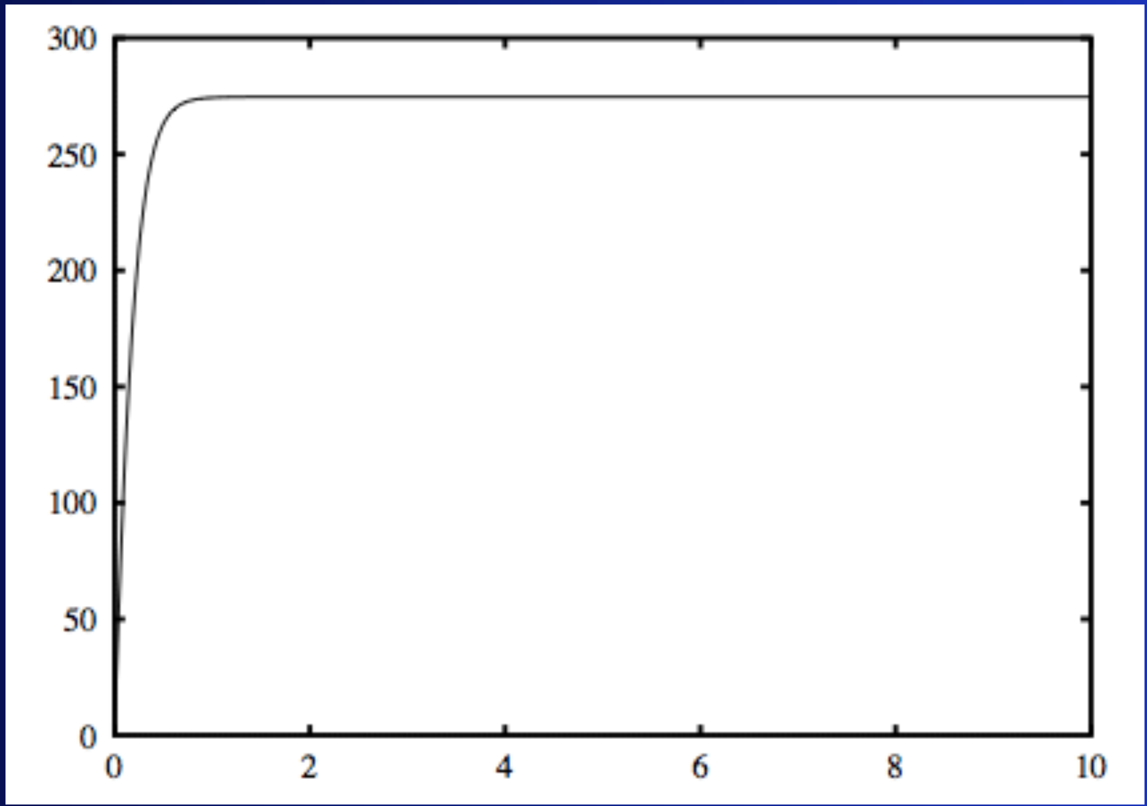


$$v_{kin} = \frac{(k_{kin}^{cat} E_{kin} M)}{(K_{m1} + M)}$$

$$v_{phos} = \frac{(k_{phos}^{kin} E_{phos} M_p)}{(K_{m2} + M_p)}$$

Without feedback: Fast equilibration

M_p



Time (seconds)

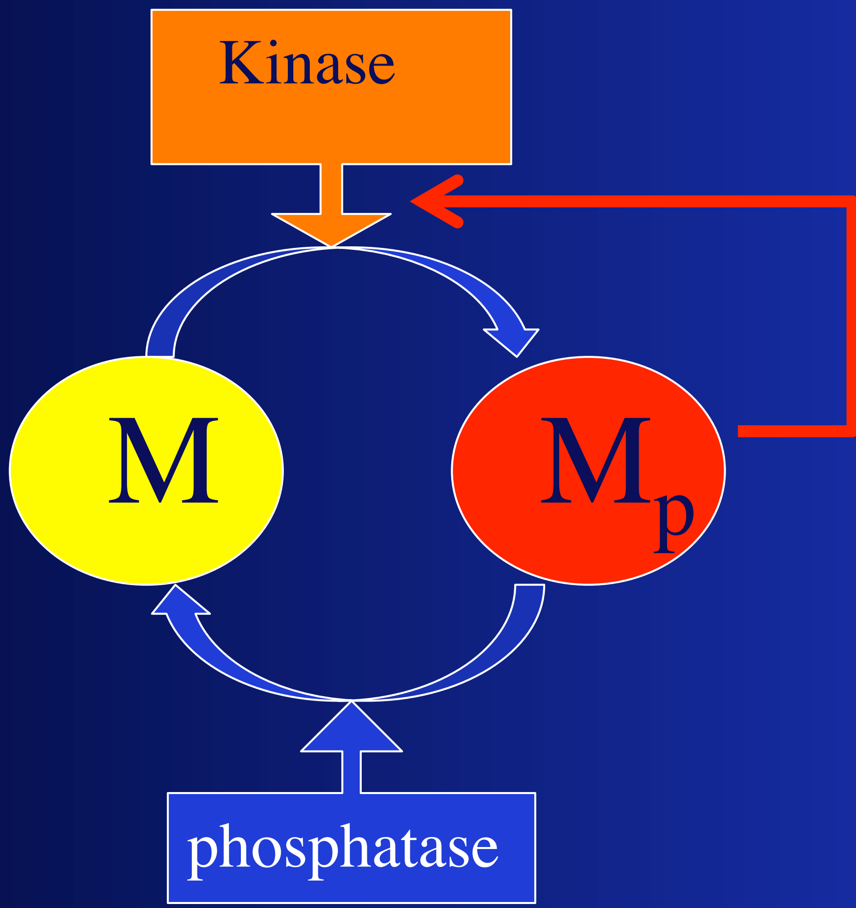
System has a single biologically relevant steady state

Feedback

We now consider a variety of feedback from the active protein Mp to the other parts of the system.

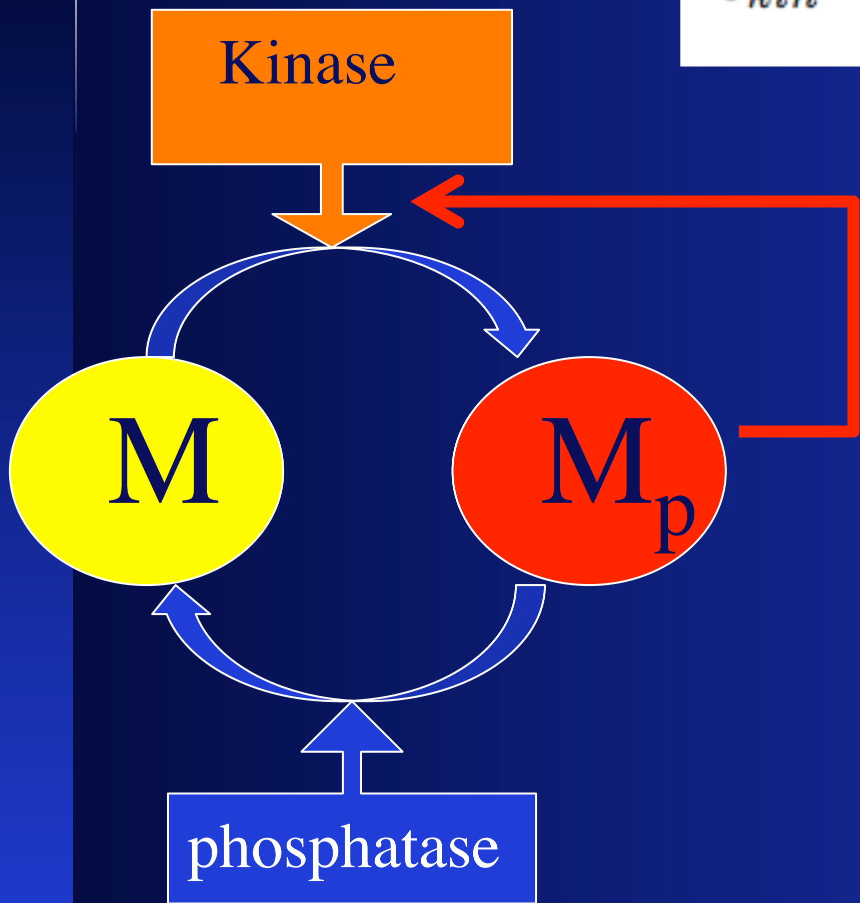
We will see that this feedback will have implications on the dynamics.

Positive feedback to kinase



Kinase rate increases as M_p increases

$$v_{kin} = \frac{(k_{kin}^{cat} E_{kin} M)}{(K_{m1} + M)} \frac{(1 + A(M_p/K_a))}{(1 + (M_p/K_a))}$$



Positive feedback term

Model equations

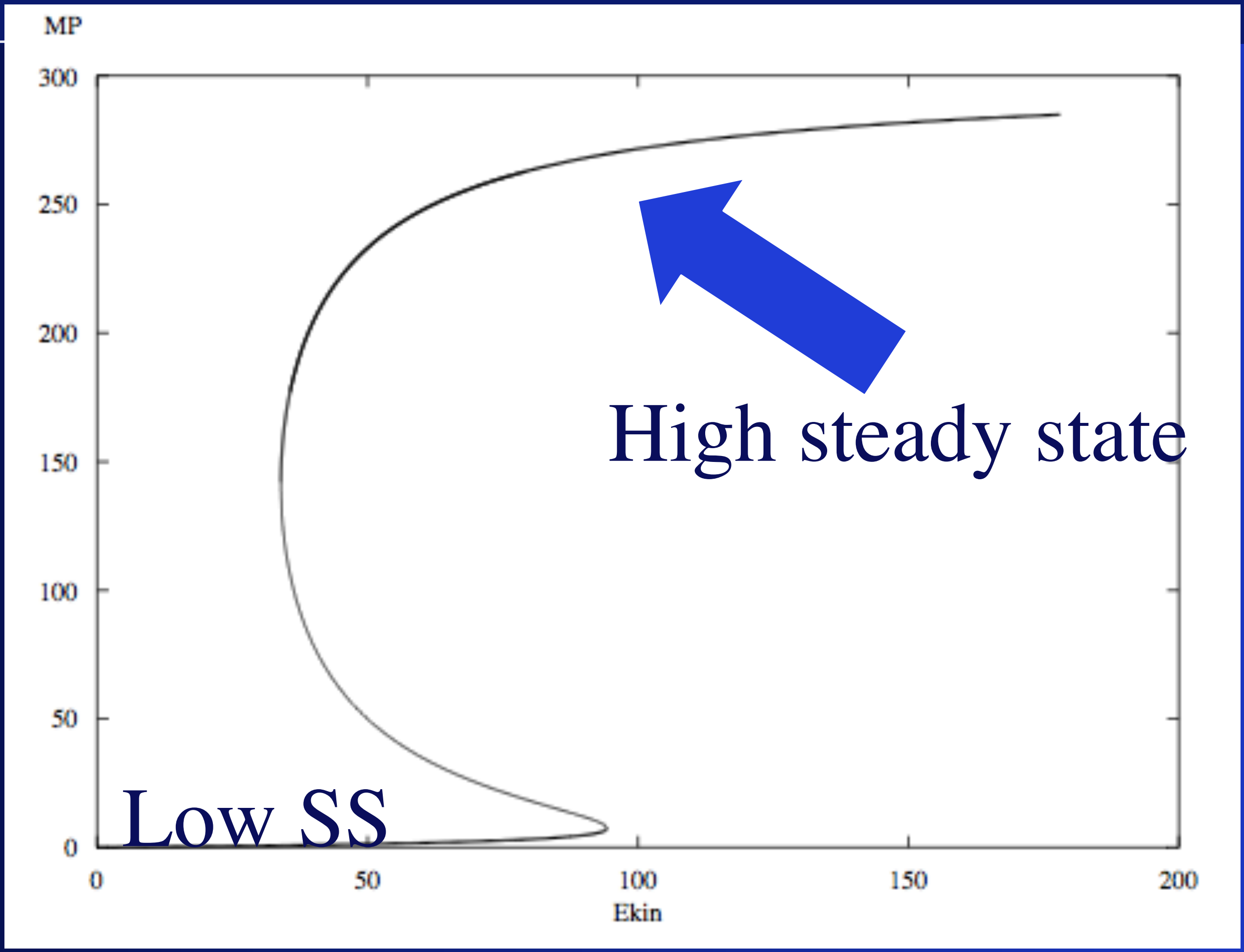
$$\frac{dM_p}{dt} = v_{kin} - v_{phos}$$

$$v_{kin} = \frac{(k_{kin}^{cat} E_{kin} M)}{(K_{m1} + M)} \frac{(1 + A(M_p/K_a))}{(1 + (M_p/K_a))}$$

$$v_{phos} = \frac{k_{phos}^{kin} E_{phos} M_p}{(K_{m2} + M_p)}$$

$$M + M_p = M_{tot}$$

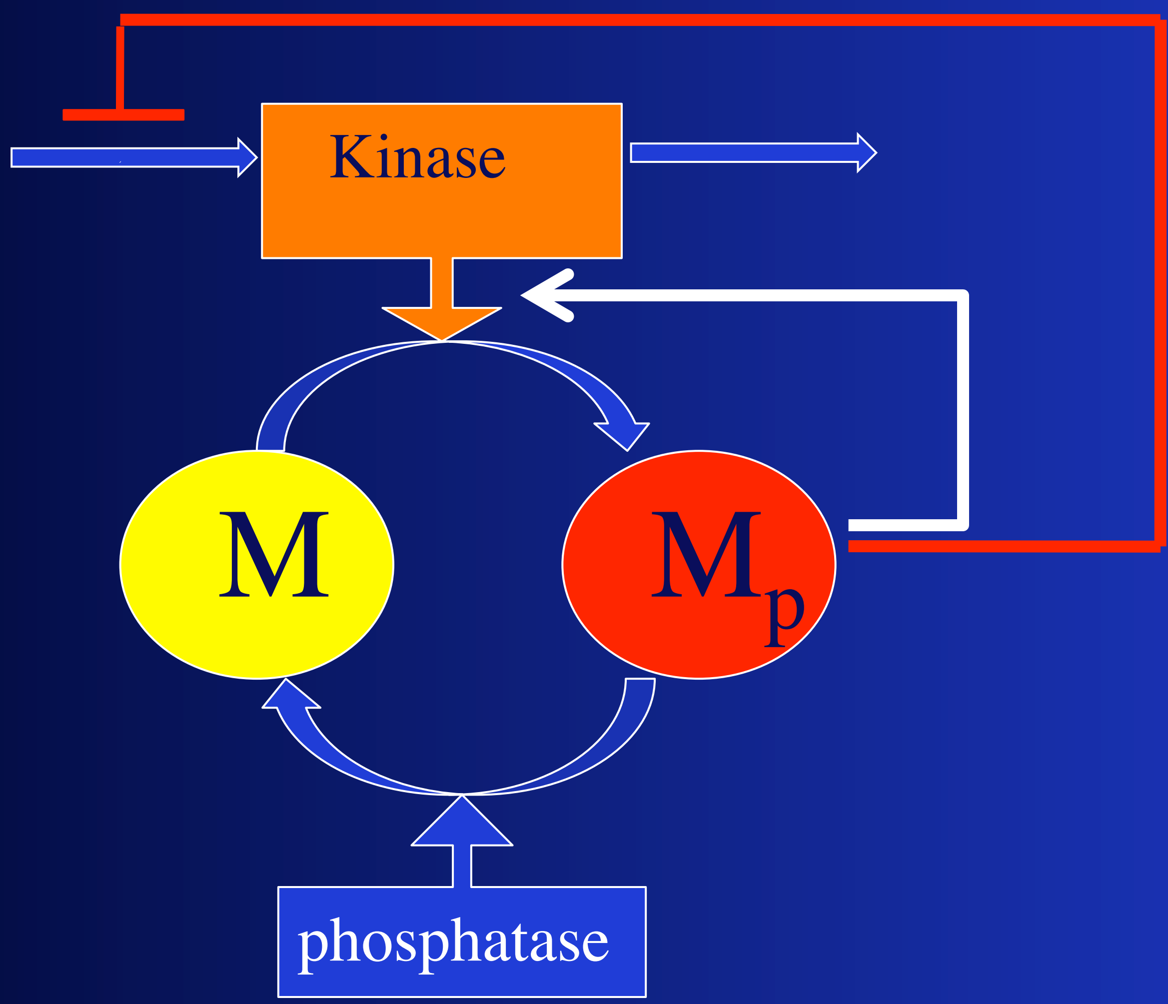
Bistable "switch"



M_p

E_{kin}

Negative feedback to kinase production rate



Now kinase is a variable

$$\frac{dE_{kin}}{dt} = v_{kin}^{synth} - v_{kin}^{deg}$$

Kinase equation:

$$\frac{dE_{kin}}{dt} = v^{synth}_{kin} - v^{deg}_{kin}$$

$$v^{deg}_{kin} = k^{deg}_{kin} E_{kin}$$

$$v^{synth}_{kin} = V^{0}_{kin} \frac{(1 + (M_p/K_l))}{(1 + I(M_p/K_l))}$$

I >1 for negative feedback

Full Model

$$\frac{dM_p}{dt} = v_{kin} - v_{phos}$$

$$\frac{dE_{kin}}{dt} = v_{kin}^{synth} - v_{kin}^{deg}$$

$$v_{kin} = \frac{(k_{kin}^{cat} E_{kin} M)}{(K_{m1} + M)} \frac{(1 + A(M_p/K_a))}{(1 + (M_p/K_a))}$$

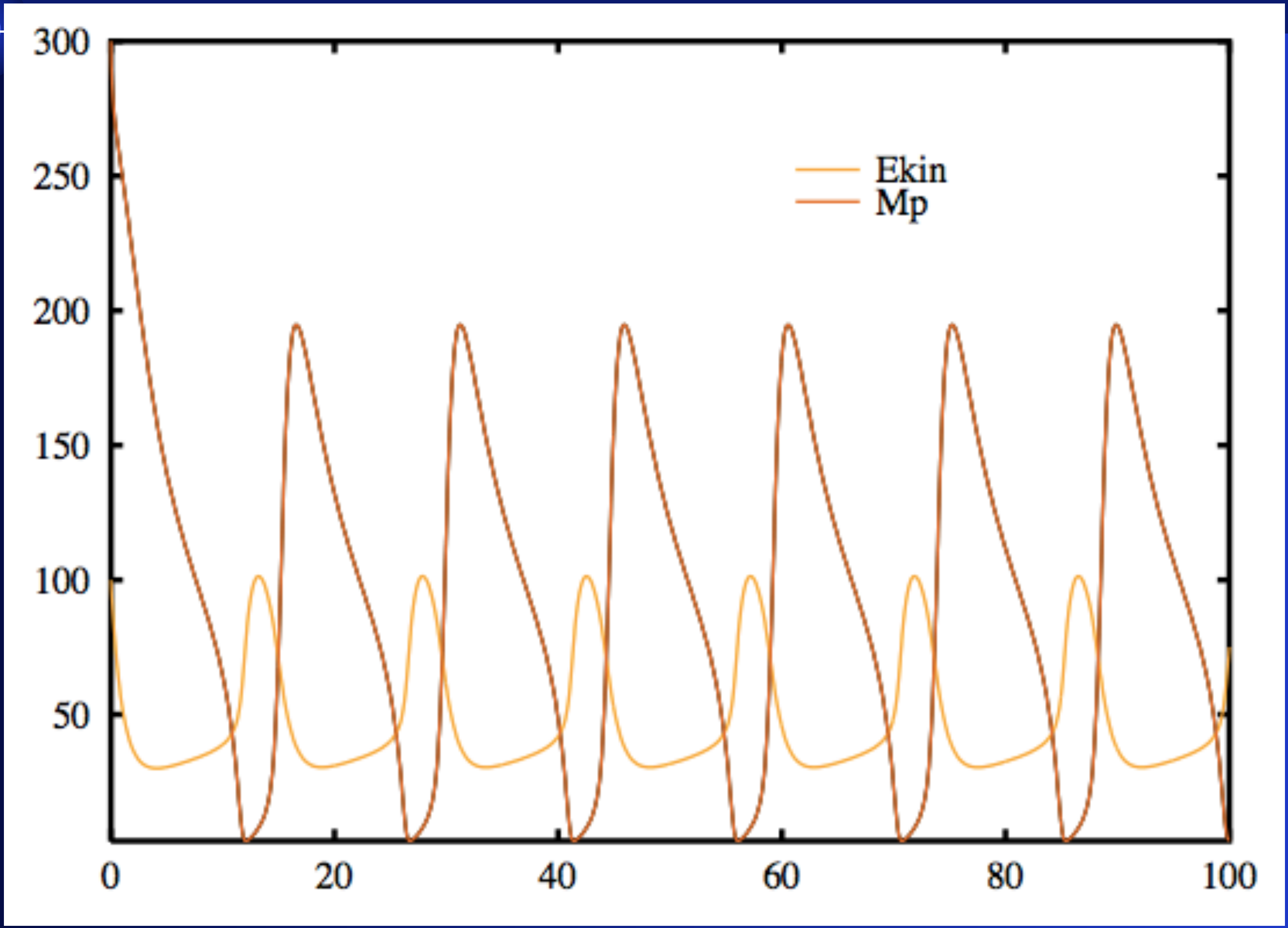
$$v_{phos} = \frac{(k_{phos}^{kin} E_{phos} M_p)}{(K_{m2} + M_p)}$$

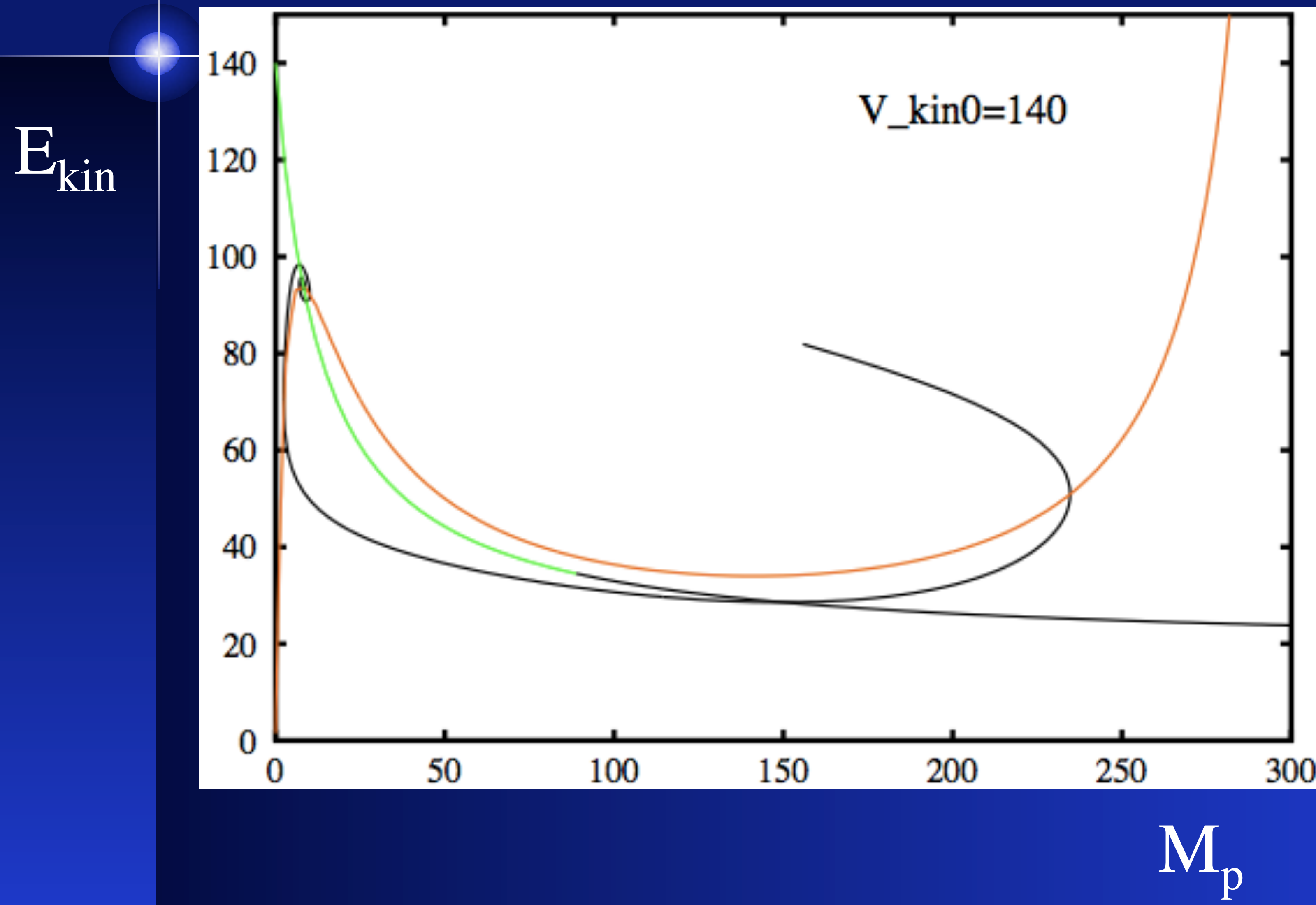
$$v_{kin}^{synth} = V_{kin}^{0} \frac{(1 + (M_p/K_l))}{(1 + I(M_p/K_l))}$$

$$v_{kin}^{deg} = k_{kin}^{deg} E_{kin}$$

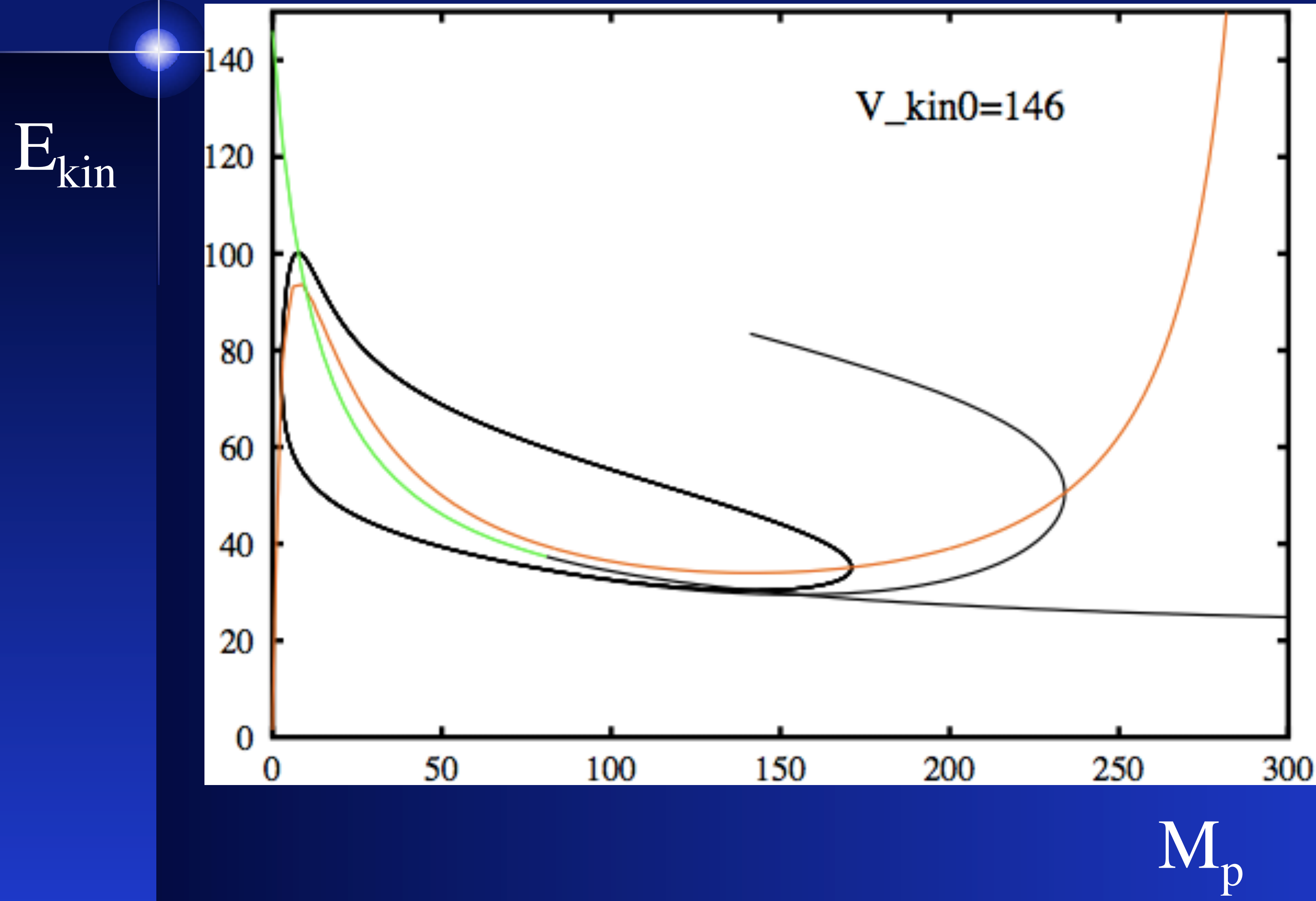
$$M + M_p = M_{tot}$$

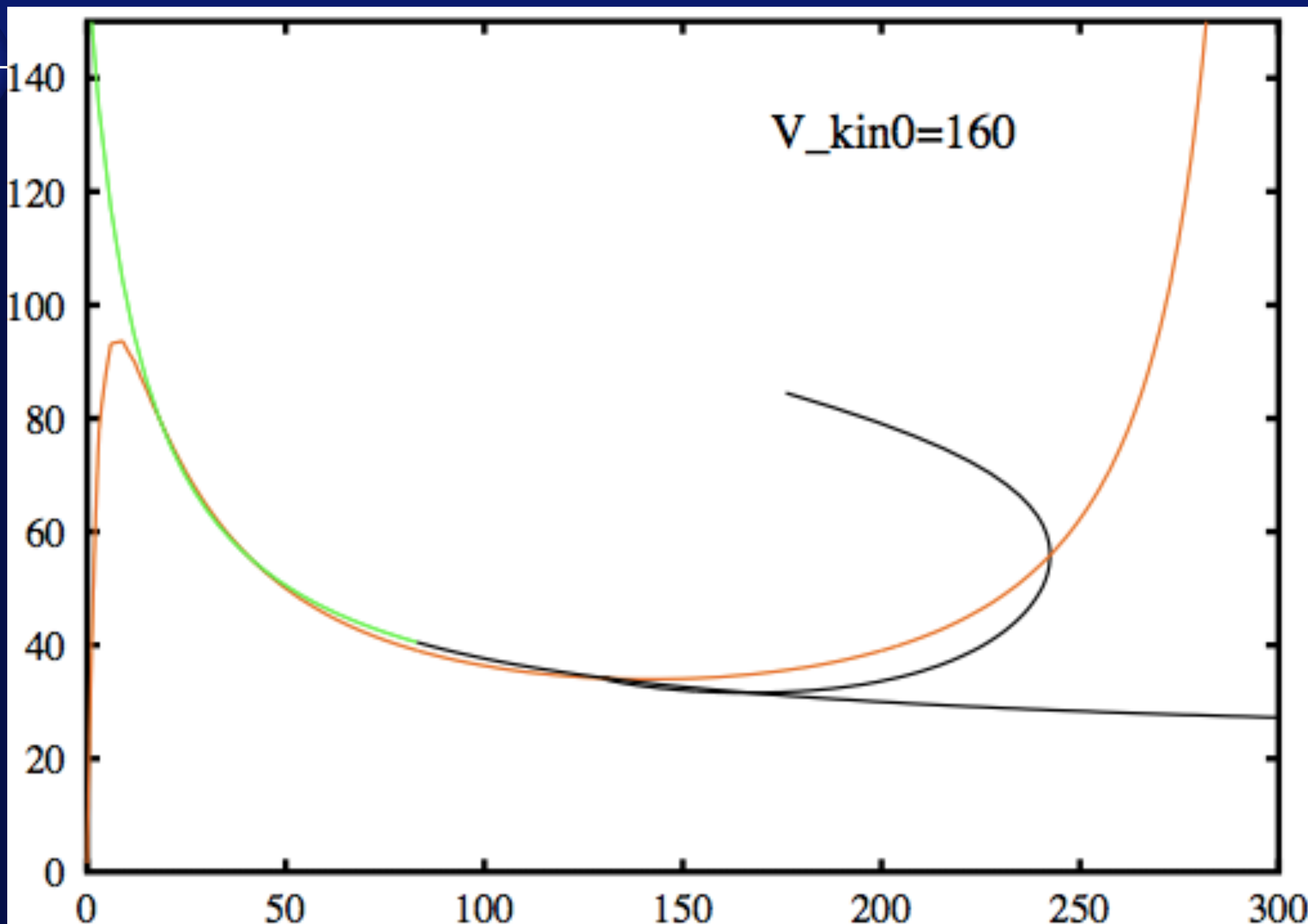
Stable cycles can be found





E_kin
M_p
V_kin0=140
0
20
40
60
80
100
120
140
0
50
100
150
200
250
300

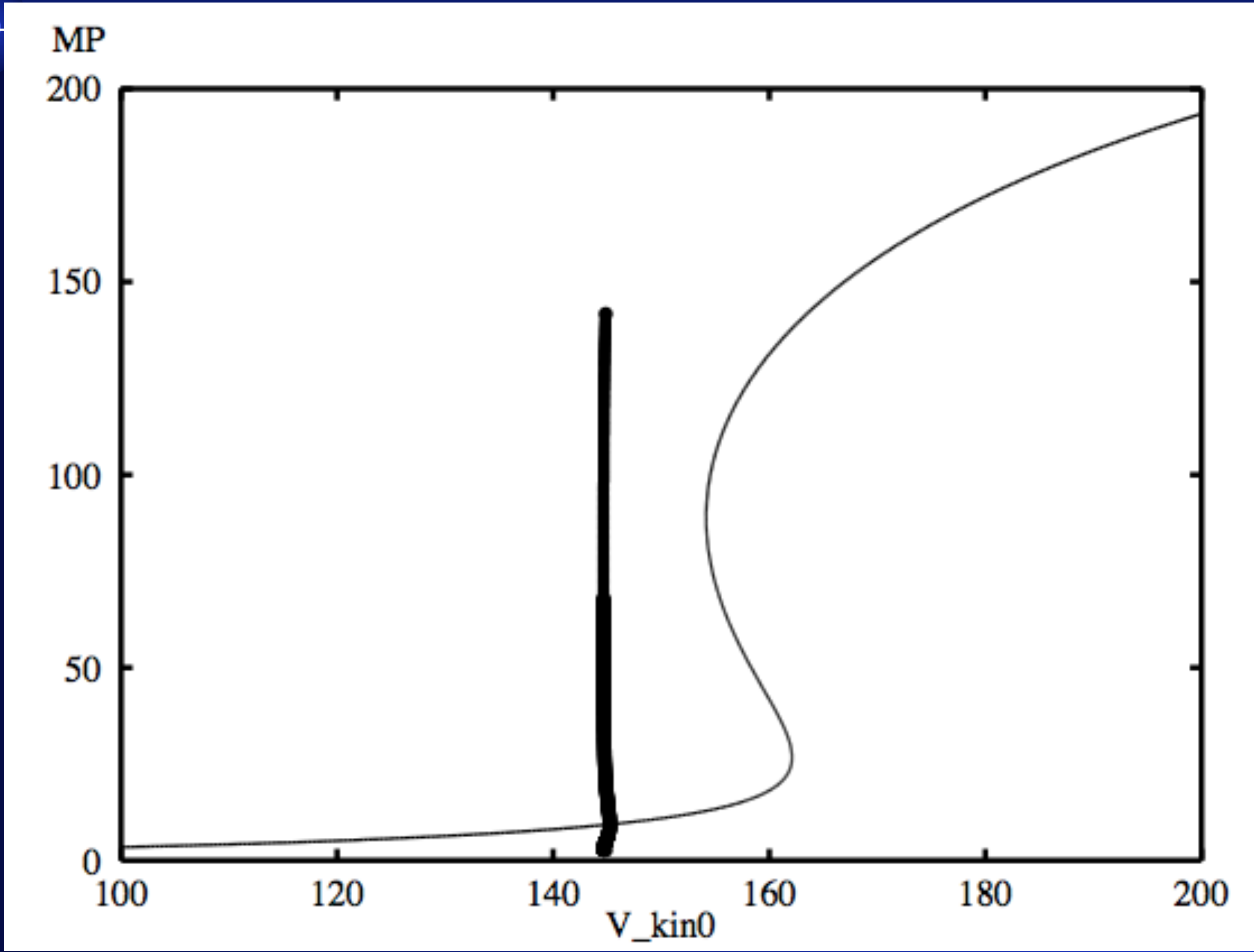

E_kin
V_kin0=146
140
120
100
80
60
40
20
0
0
50
100
150
200
250
300
M_p



E_{kin}

M_p

Bifurcation diagram



Zoom view: Hopf Bifurcation