Supply and demand in Metabolic Control Theory

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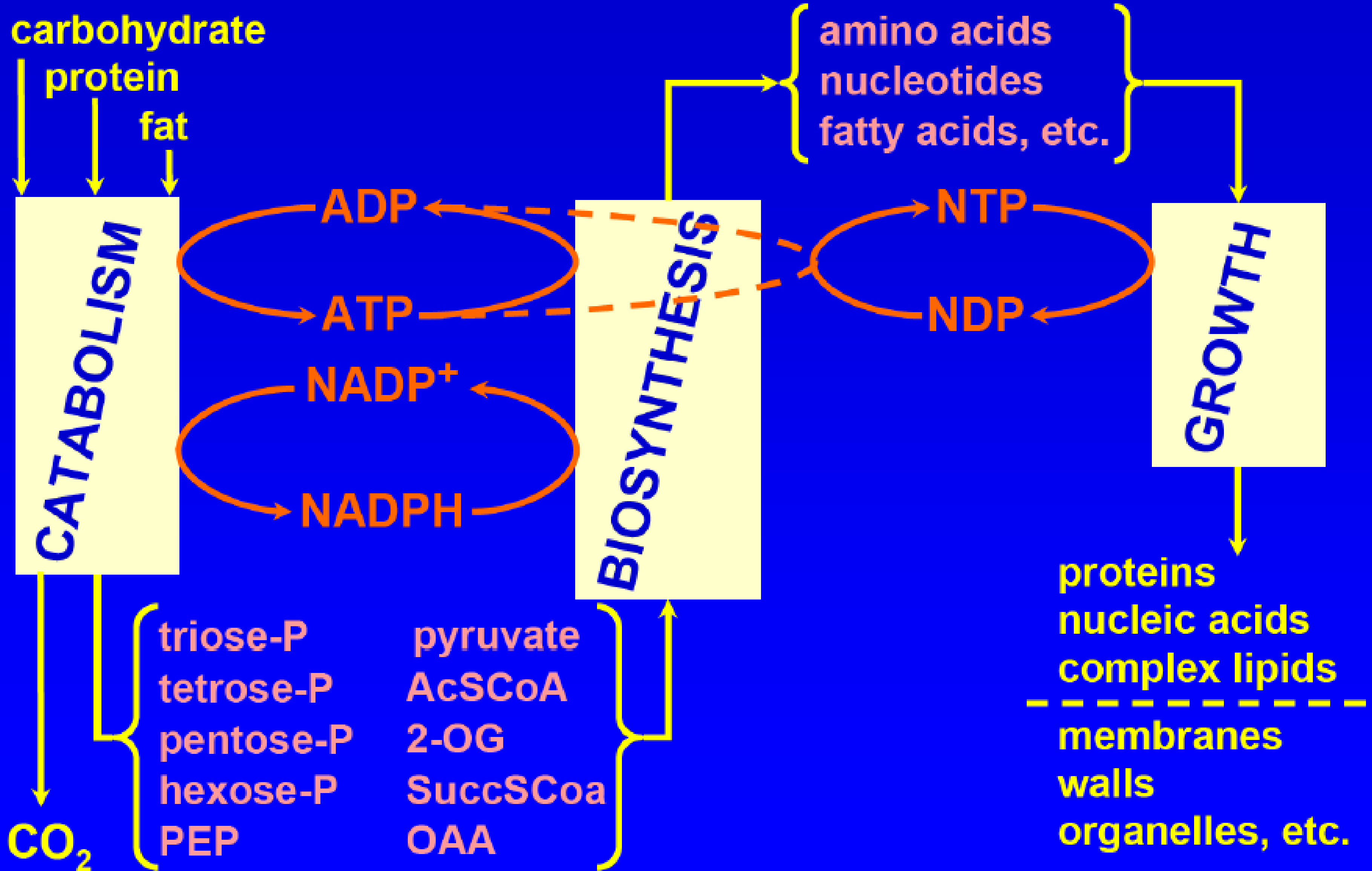
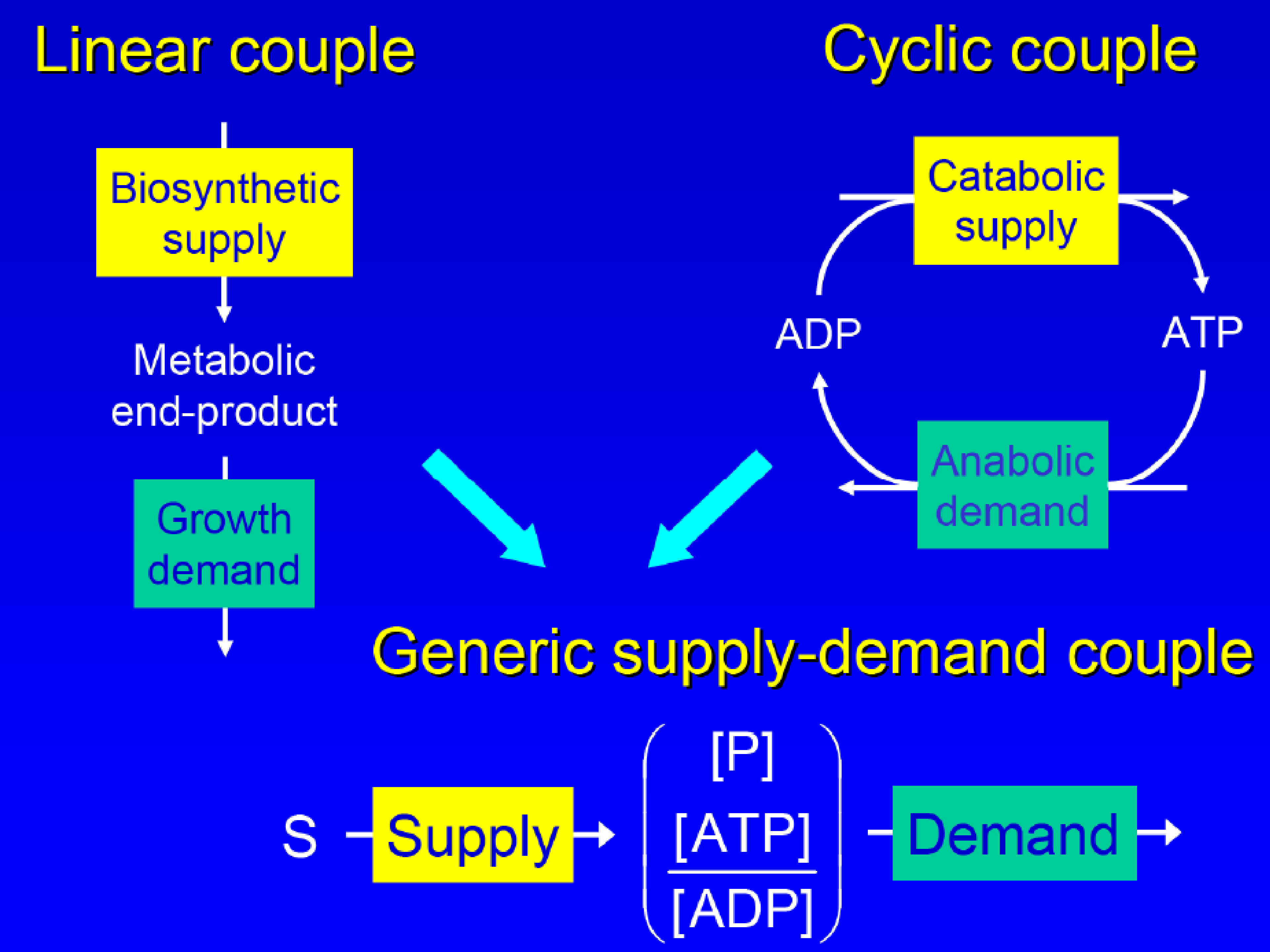
Slides borrowed from Jannie Hofmeyr
Stellenbosch University

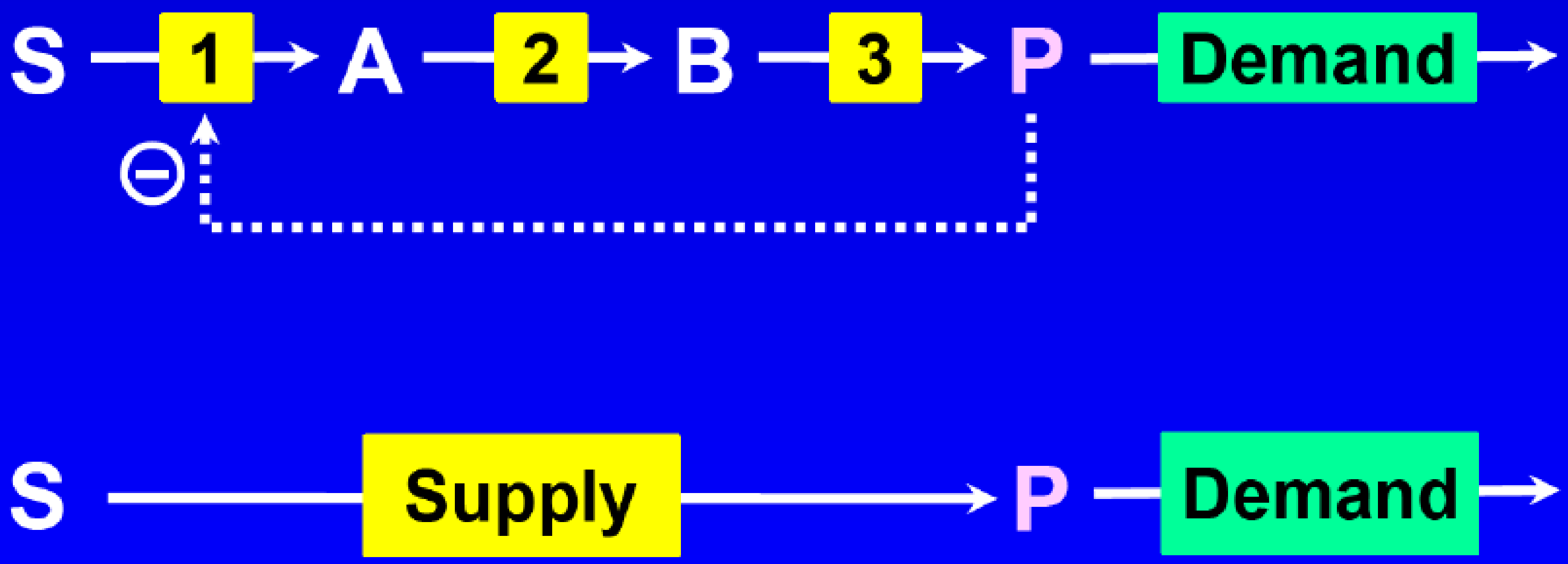
Hofmeyr & Cornish-Bowden (2000) *FEBS Lett.* 476:47-51

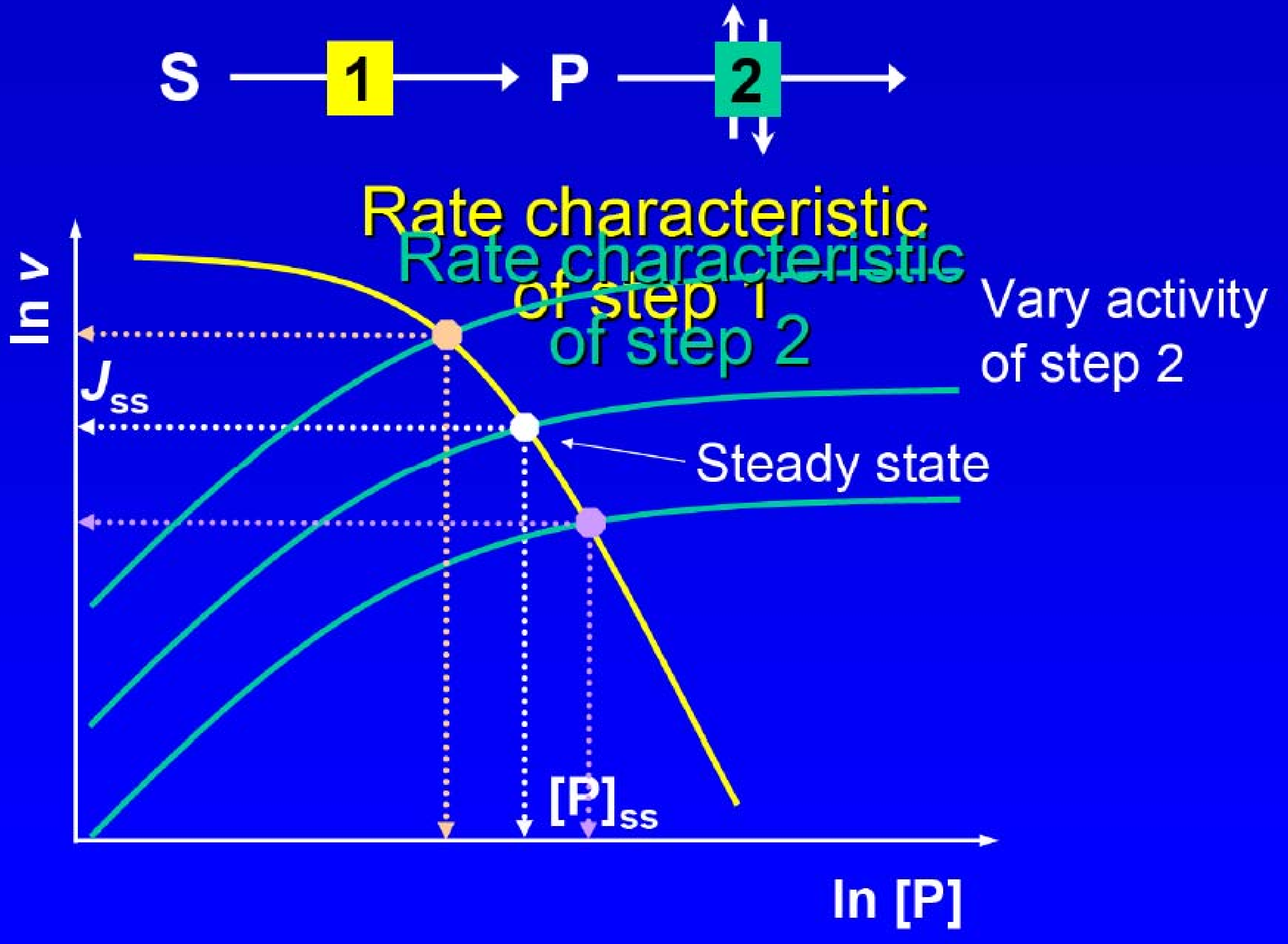
Functional organisation of metabolism



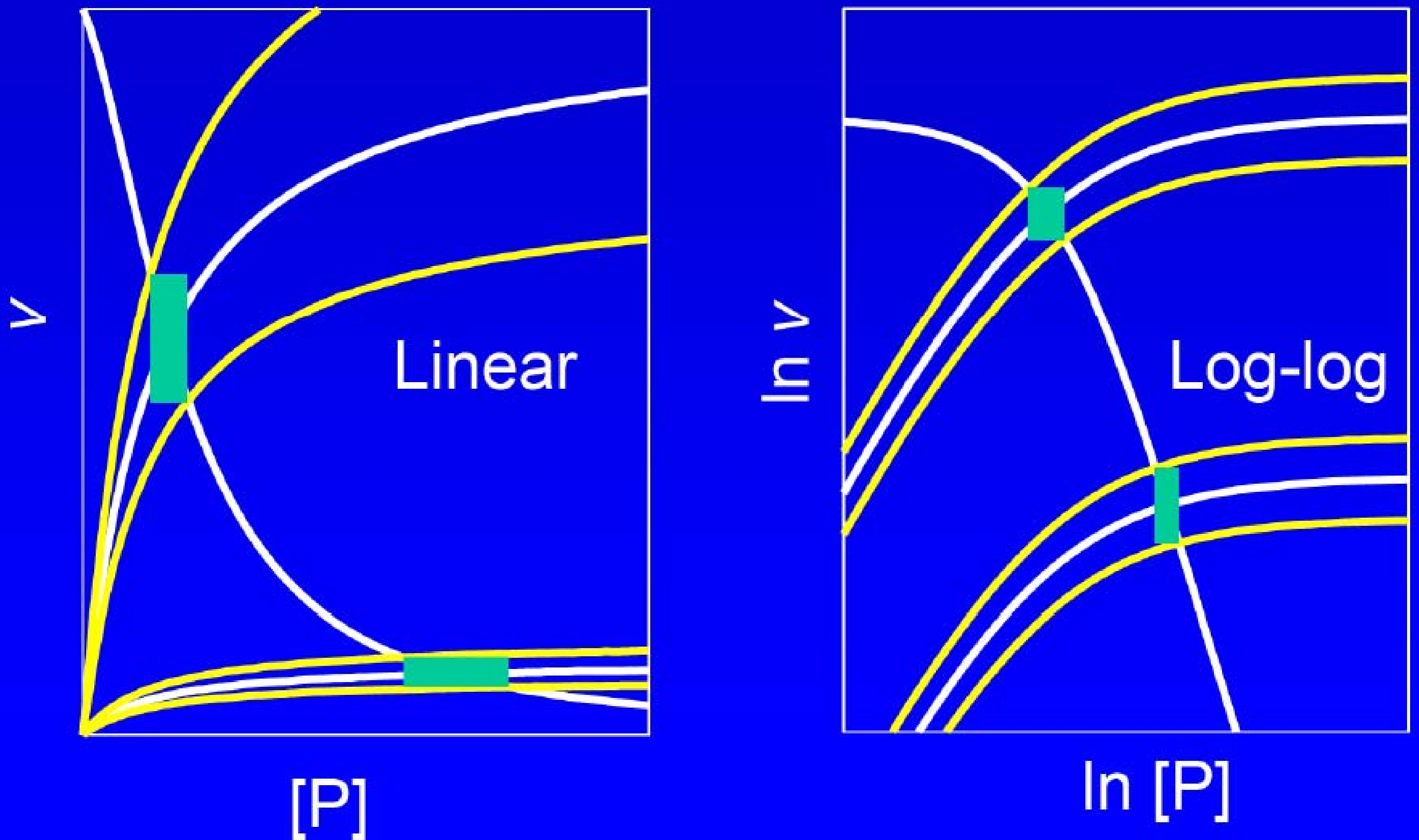

Linear couple
Cyclic couple
Biosynthetic supply
Metabolic end-product
Growth demand
Catabolic supply
ADP
ATP
Anabolic demand
Generic supply-demand couple
S
Supply
[P]
[ATP]
[ADP]
Demand

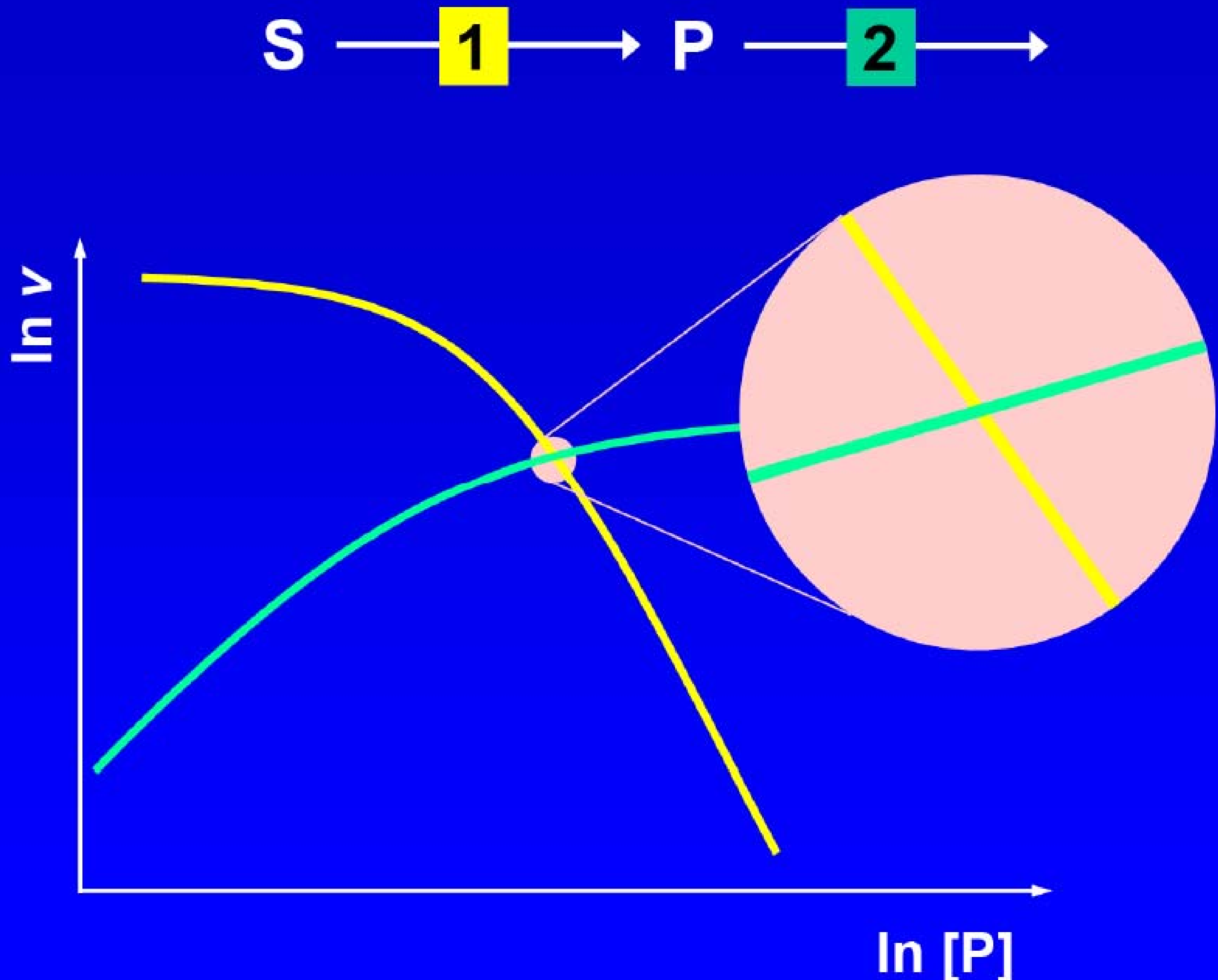
Starting point:
a metabolic factory

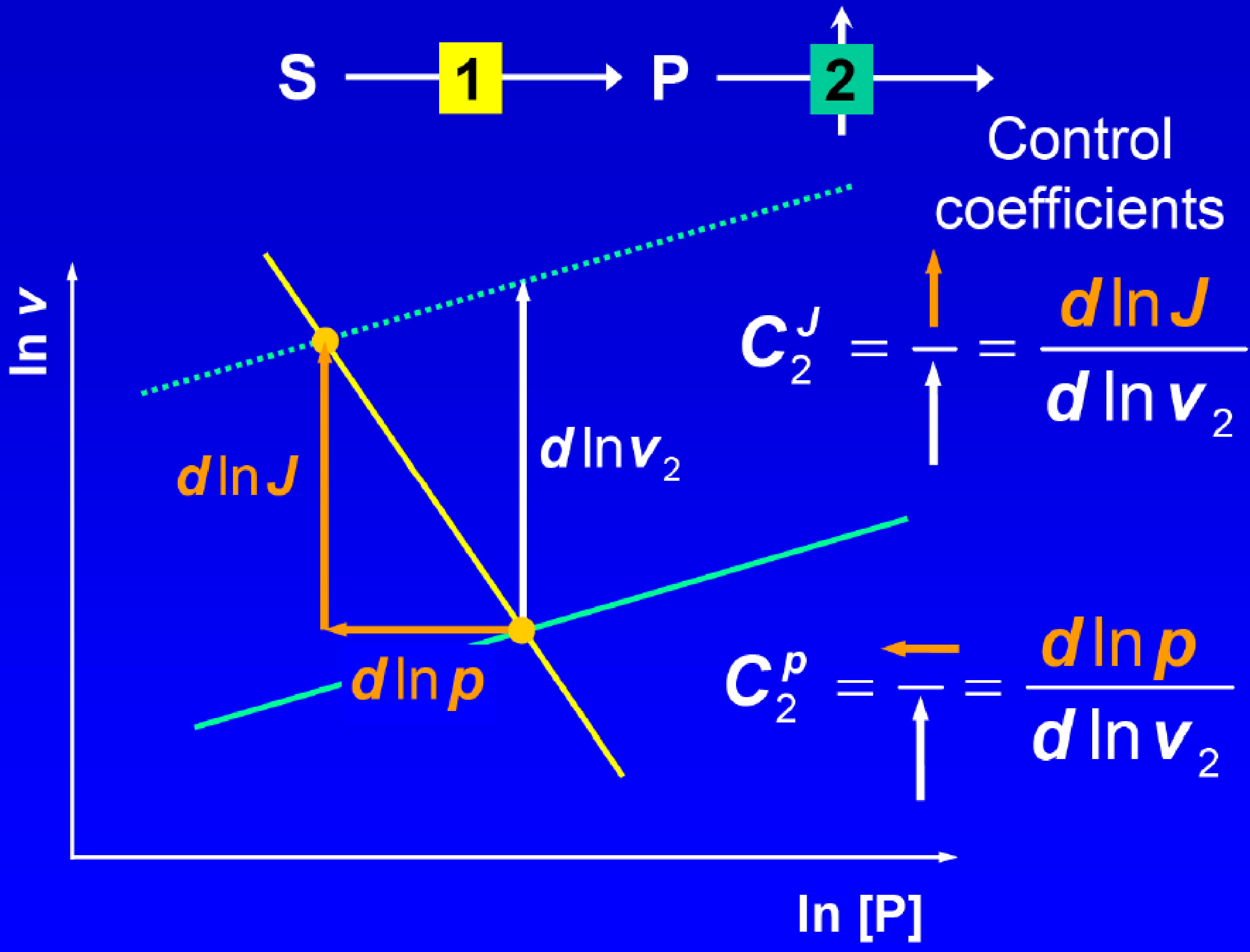


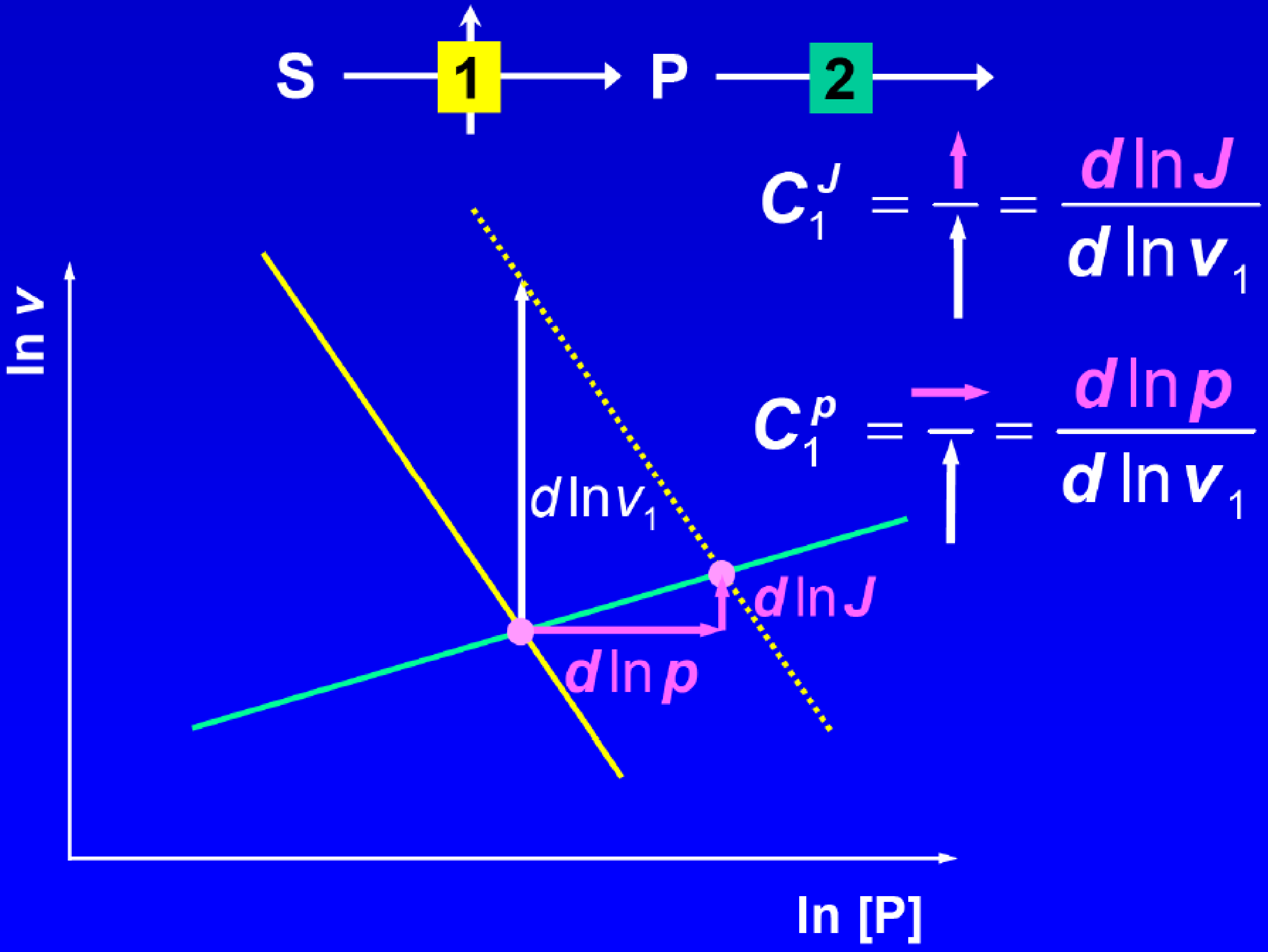

S
1
P
2
Rate characteristic
of step 1
Rate characteristic
of step 2
Vary activity
of step 2
ln v
J_{ss}
Steady state
$[P]_{ss}$
ln [P]

Linear vs. Logarithmic rate characteristics

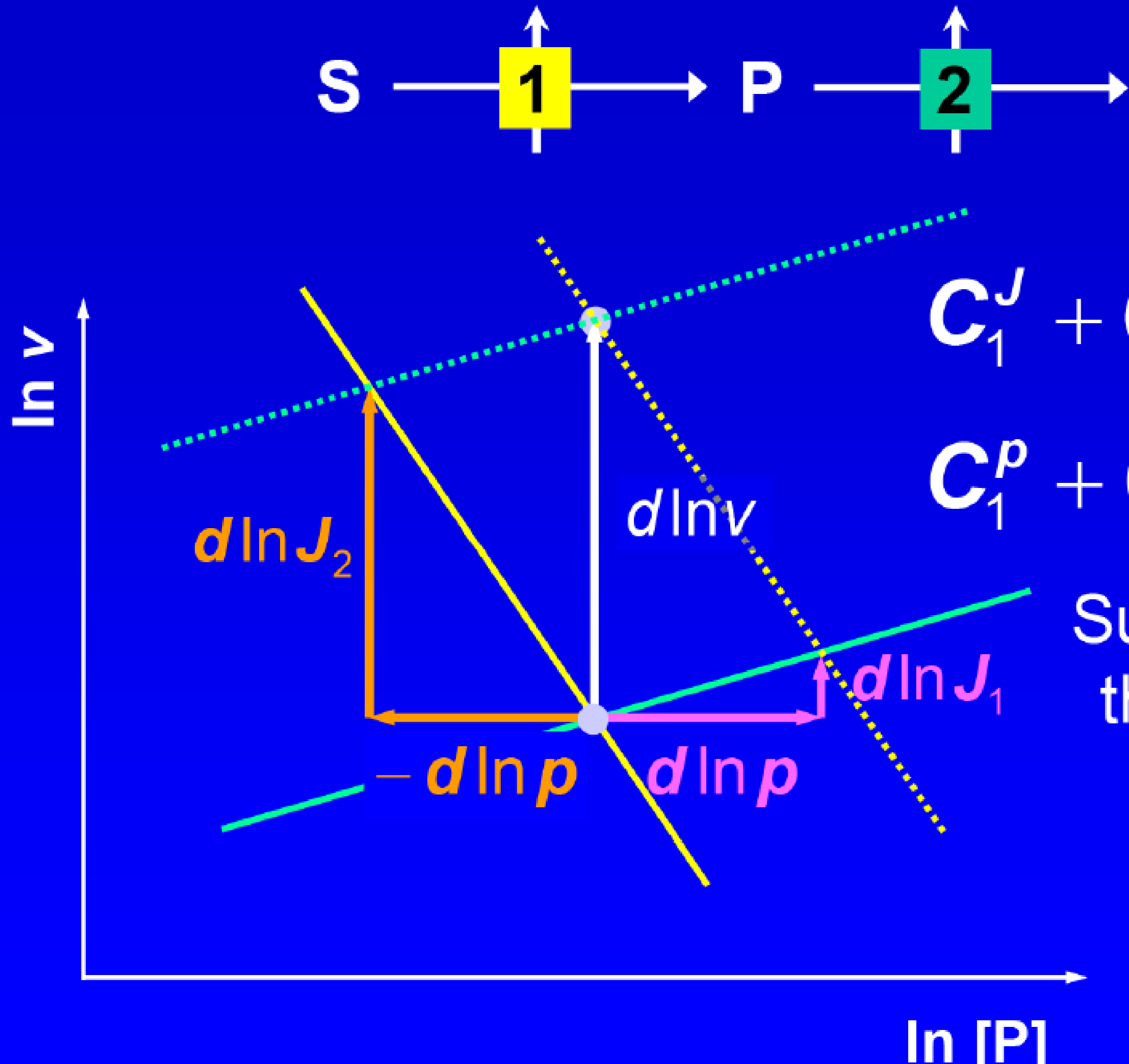



S
1
P
2
ln v
ln [P]


S
1
P
2
Control coefficients
ln v
ln [P]
d ln J
d ln v2
d ln p
$C_2^J = \frac{\uparrow}{\uparrow} = \frac{d \ln J}{d \ln v_2}$
$C_2^p = \frac{\leftarrow}{\uparrow} = \frac{d \ln p}{d \ln v_2}$



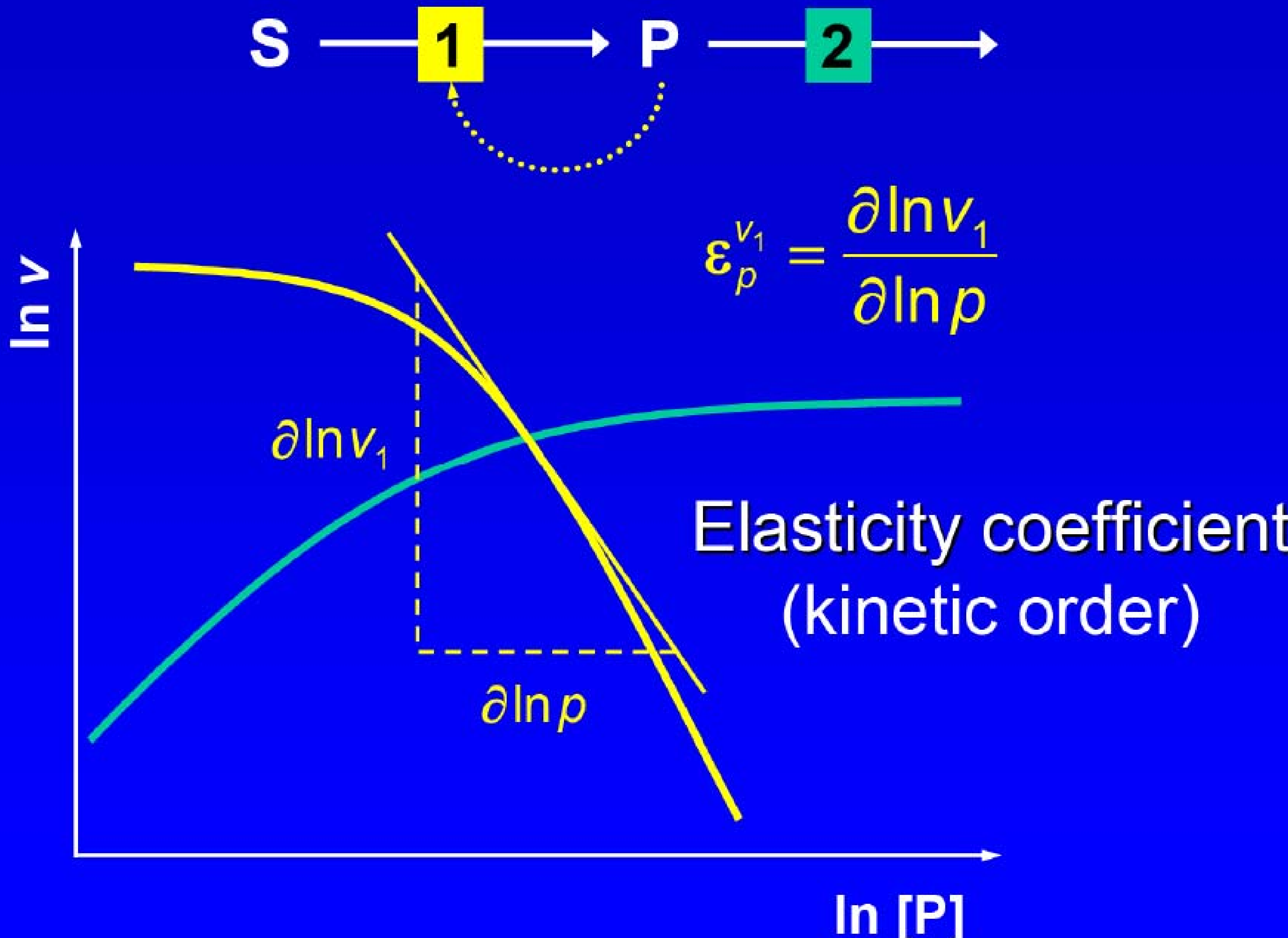
S
1
P
2
$C_1^J = \frac{\uparrow}{\uparrow} = \frac{d \ln J}{d \ln v_1}$
$C_1^p = \frac{\rightarrow}{\uparrow} = \frac{d \ln p}{d \ln v_1}$
ln v
$d \ln v_1$
$d \ln J$
$d \ln p$
ln [P]

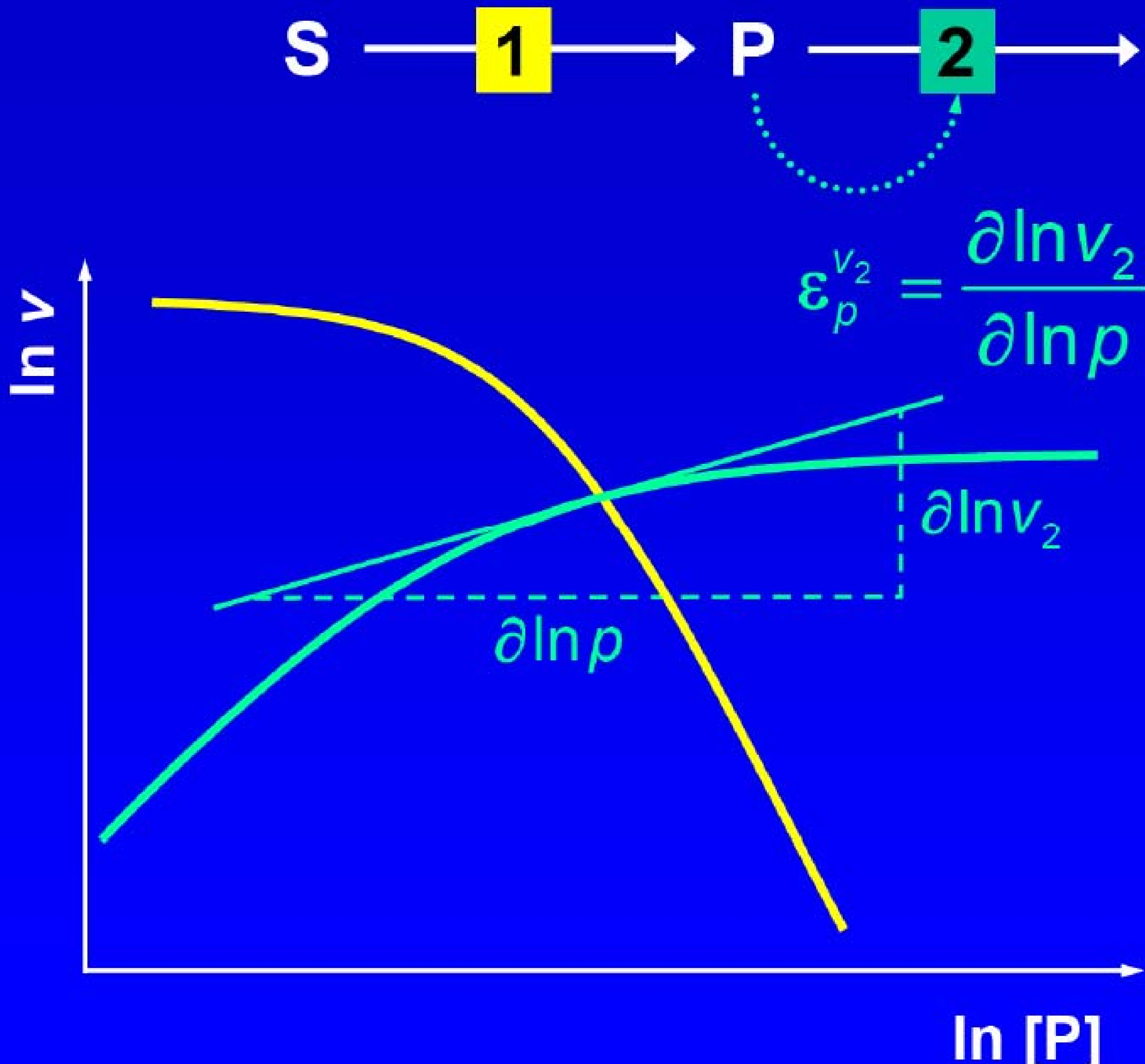


$$C_1^J + C_2^J = 1$$

$$C_1^p + C_2^p = 0$$

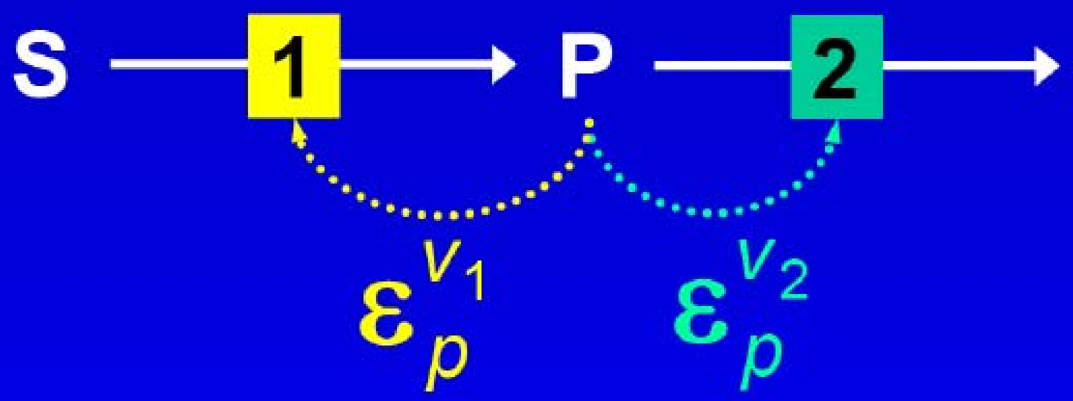
Summation theorems


S
1
P
2
ln v
ln [P]
$\partial \ln v_1$
$\partial \ln p$
$\varepsilon_p^{v_1} = \frac{\partial \ln v_1}{\partial \ln p}$
Elasticity coefficient
(kinetic order)



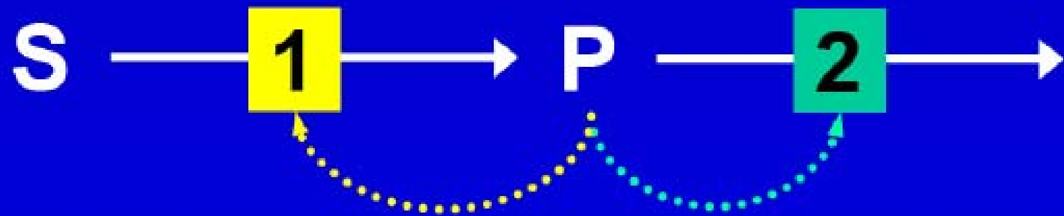
S
1
P
2
$\varepsilon_p^{v_2} = \frac{\partial \ln v_2}{\partial \ln p}$
ln v
$\partial \ln v_2$
$\partial \ln p$
ln [P]

Summary of Control Properties



	Summation	Connectivity
Flux	$C_1^J + C_2^J = 1$	$C_1^J \varepsilon_p^{v_1} + C_2^J \varepsilon_p^{v_2} = 0$
Concen-tration	$C_1^p + C_2^p = 0$	$C_1^p \varepsilon_p^{v_1} + C_2^p \varepsilon_p^{v_2} = -1$

Control analytic expressions

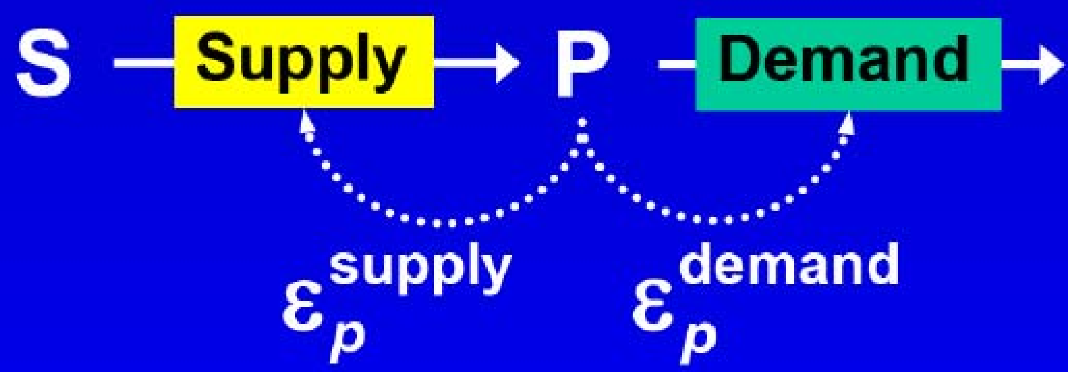


$$\varepsilon_p^{v_1} \qquad \varepsilon_p^{v_2}$$

$$C_1^J = \frac{\varepsilon_p^{v_2}}{\varepsilon_p^{v_2} - \varepsilon_p^{v_1}} \qquad C_2^J = \frac{-\varepsilon_p^{v_1}}{\varepsilon_p^{v_2} - \varepsilon_p^{v_1}}$$

$$C_1^p = \frac{1}{\varepsilon_p^{v_2} - \varepsilon_p^{v_1}} \qquad C_2^p = \frac{-1}{\varepsilon_p^{v_2} - \varepsilon_p^{v_1}}$$

Control analysis of supply and demand



$$C^J_{supply} = \frac{\varepsilon_p^{demand}}{\varepsilon_p^{demand} - \varepsilon_p^{supply}} \qquad C^J_{demand} = \frac{-\varepsilon_p^{supply}}{\varepsilon_p^{demand} - \varepsilon_p^{supply}}$$

$$C^p_{supply} = \frac{1}{\varepsilon_p^{demand} - \varepsilon_p^{supply}} \qquad C^p_{demand} = \frac{-1}{\varepsilon_p^{demand} - \varepsilon_p^{supply}}$$

Distribution of flux control is determined by the RATIO of supply and demand elasticities

$$\frac{C^J_{\text{demand}}}{C^J_{\text{supply}}} = \frac{-\varepsilon_p^{\text{supply}}}{\varepsilon_p^{\text{demand}}}$$

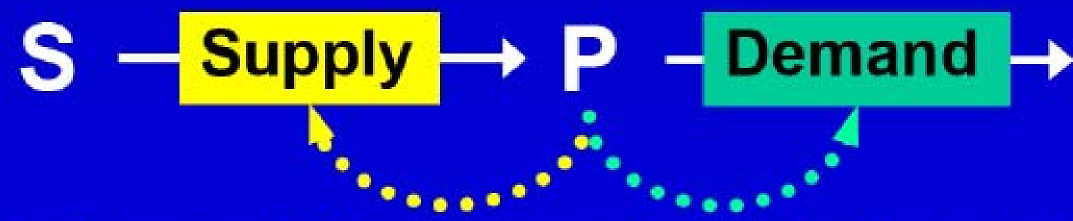
Case

$$\varepsilon_p^{\text{demand}} << \left|\varepsilon_p^{\text{supply}}\right|$$

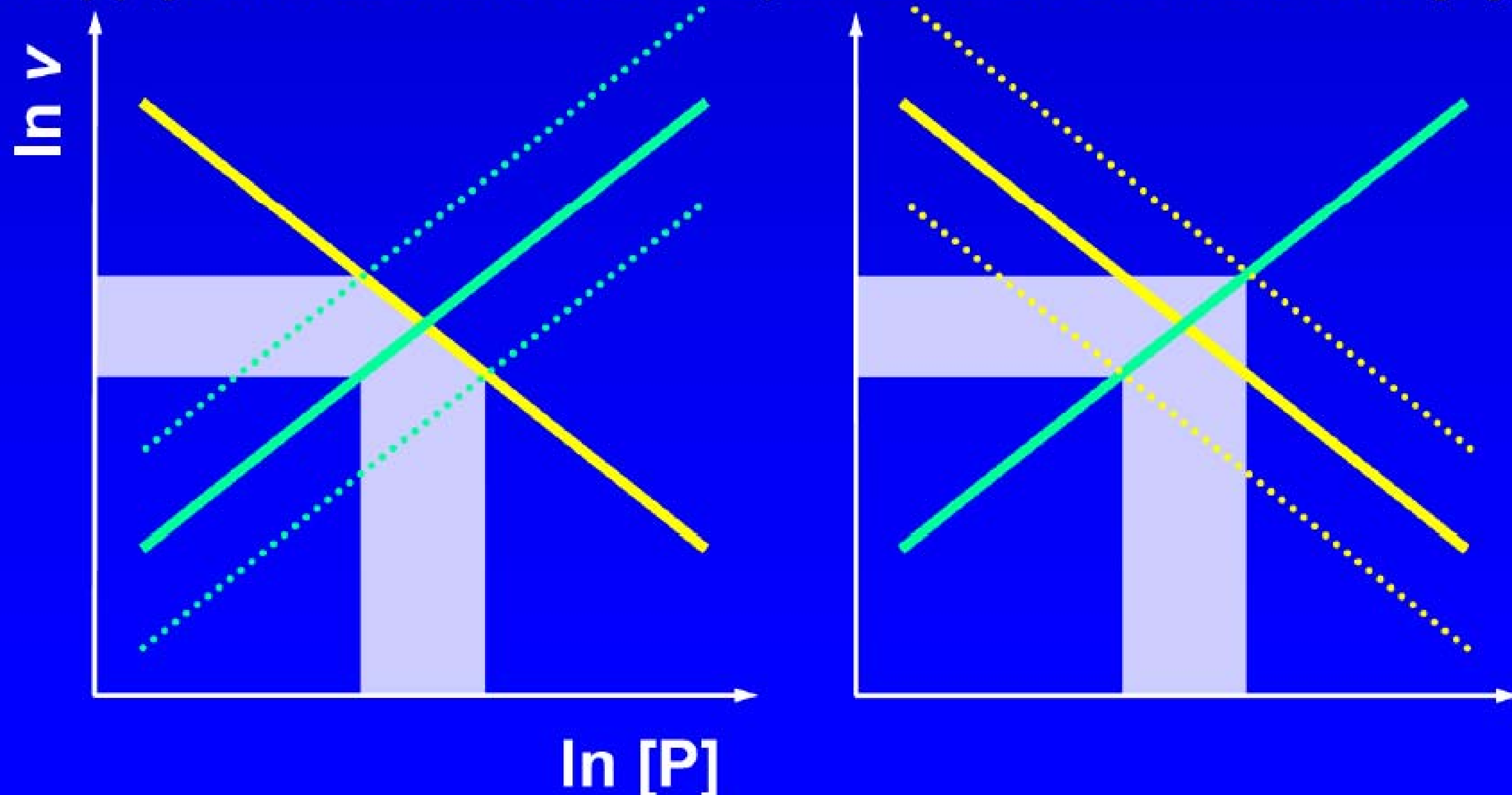
$$\Rightarrow C^J_{\text{demand}} >> C^J_{\text{supply}}$$

$$\Rightarrow C^J_{\text{demand}} \approx 1$$

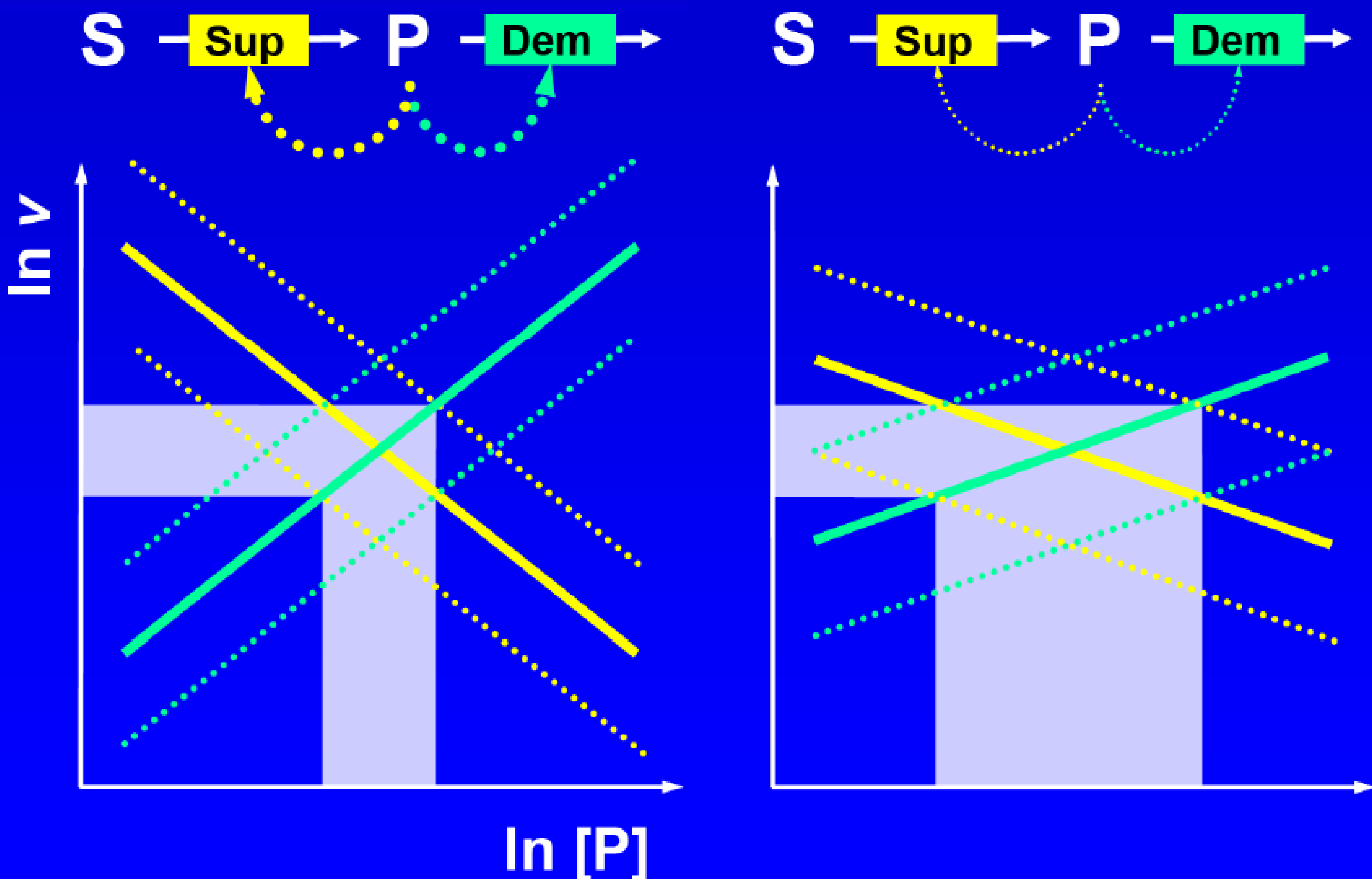
A functionally undifferentiated system



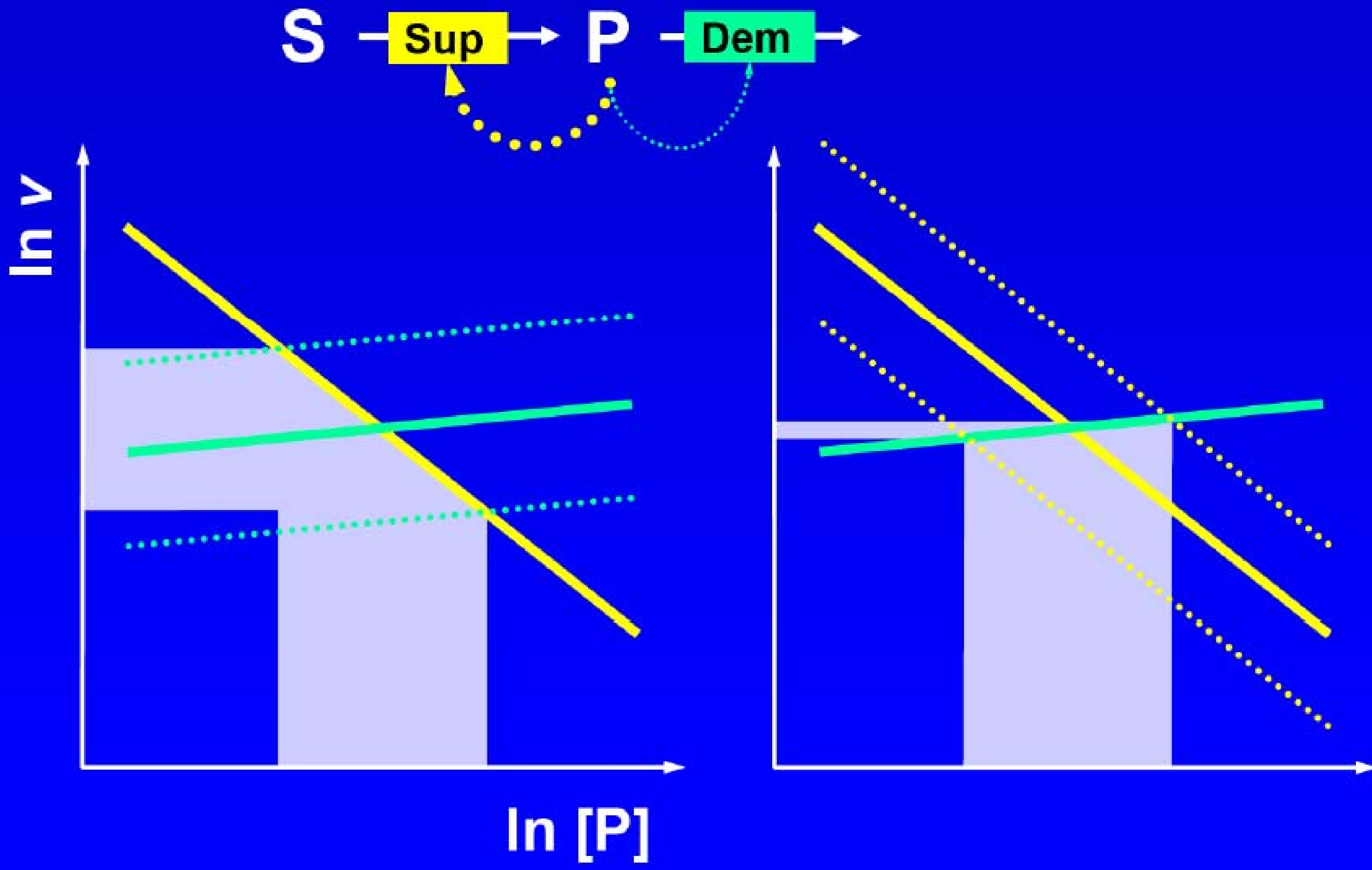
Supply and demand have equal control over flux and [P]



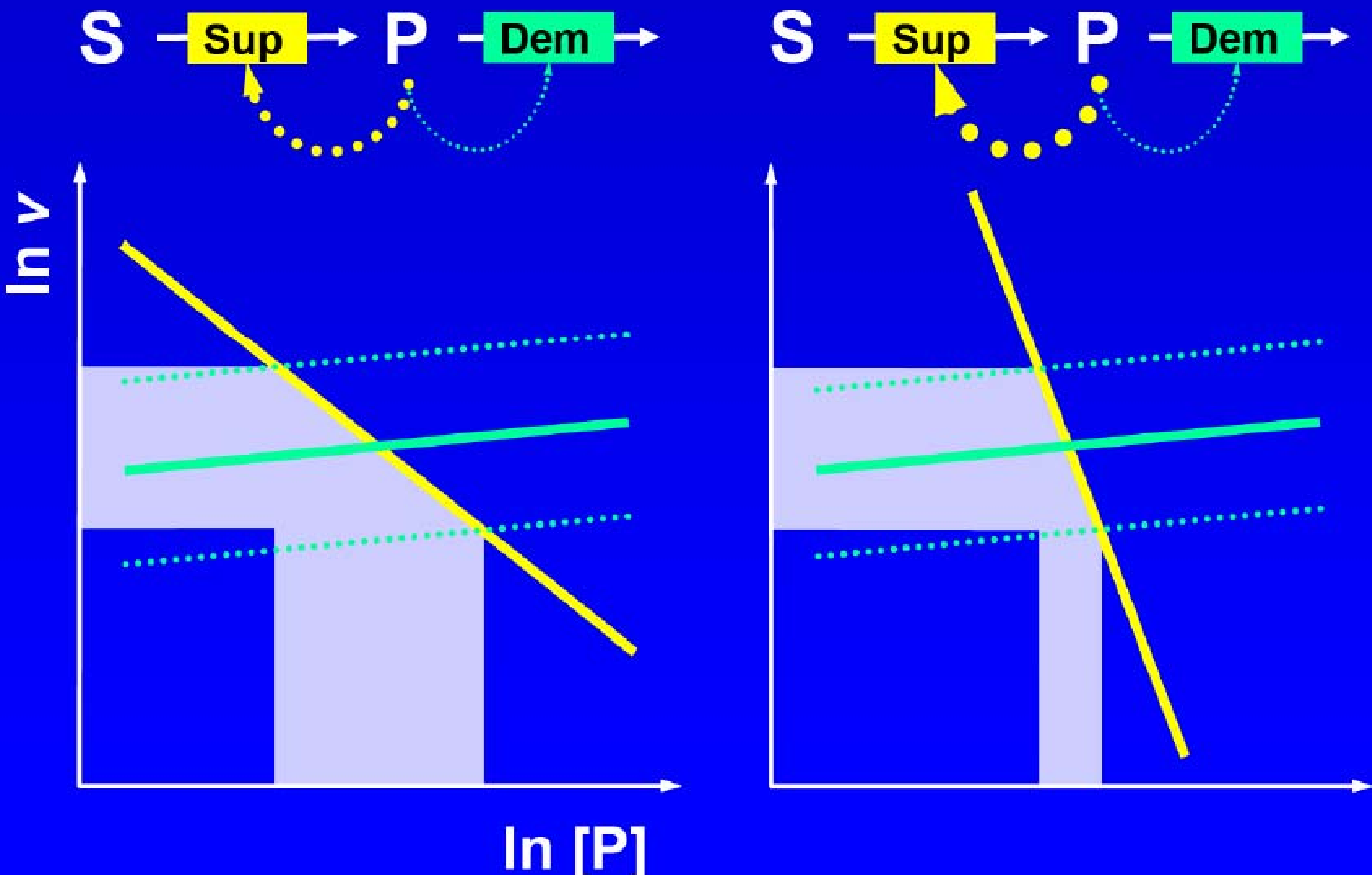
The sum of slopes determines the magnitude of concentration control



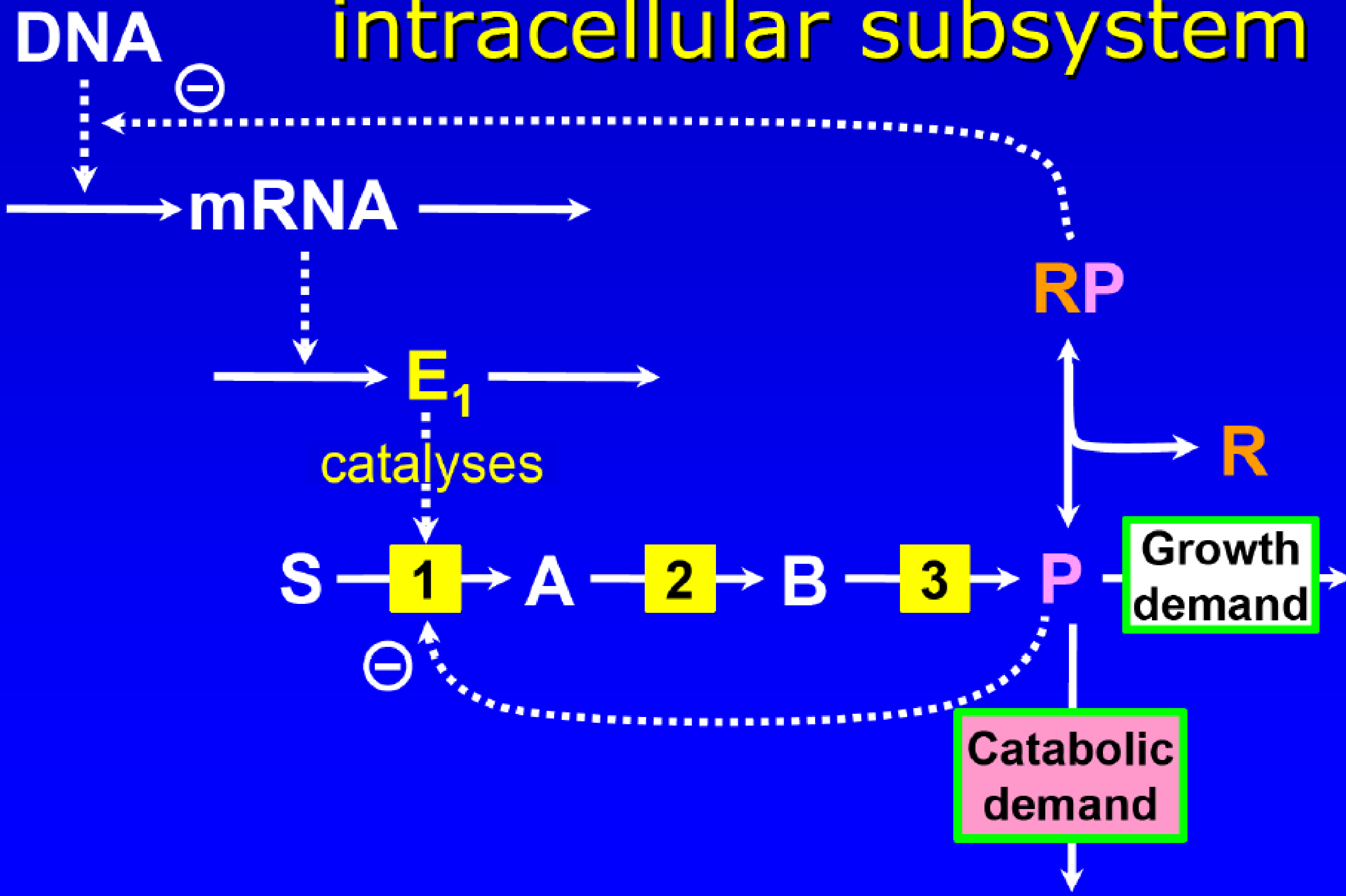
If the supply/demand slope ratio > 1, then flux-control shifts to the demand



The more one block controls the flux, the more the other determines the magnitude of P-control



A typical regulated intracellular subsystem

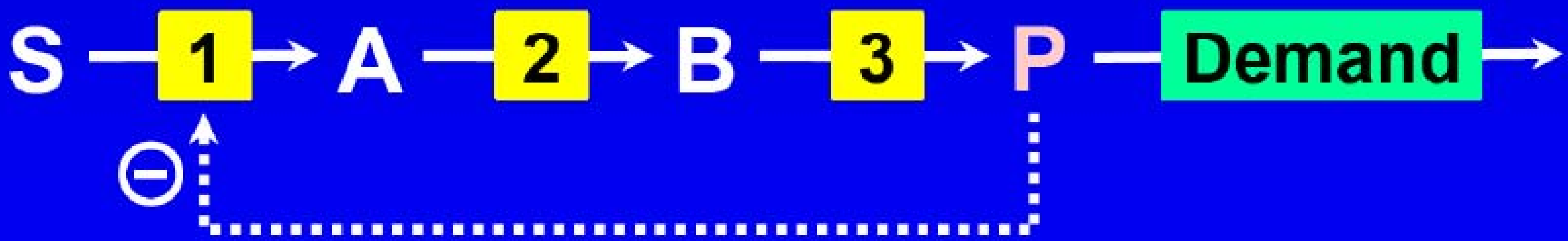


Modelling the biosynthetic supply

Reversible Hill-equation with modifier P

Reversible Michaelis-Menten equations

Irreversible Michaelis-Menten equation



$K_{eq} = 400$ $K_{eq} = 10$ $K_{eq} = 10$

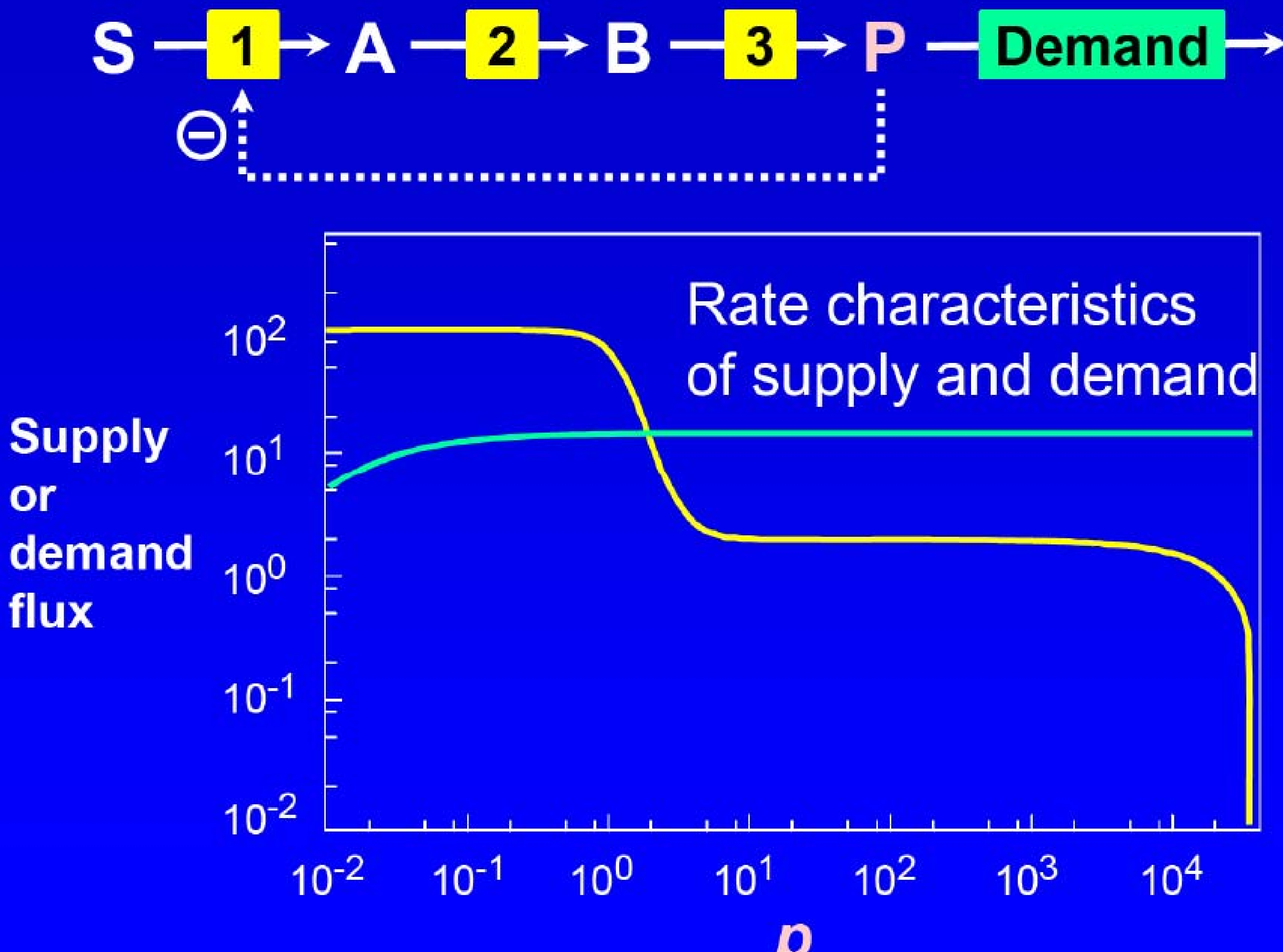
Equilibrium concentrations

1 **400** **4000** **40000**

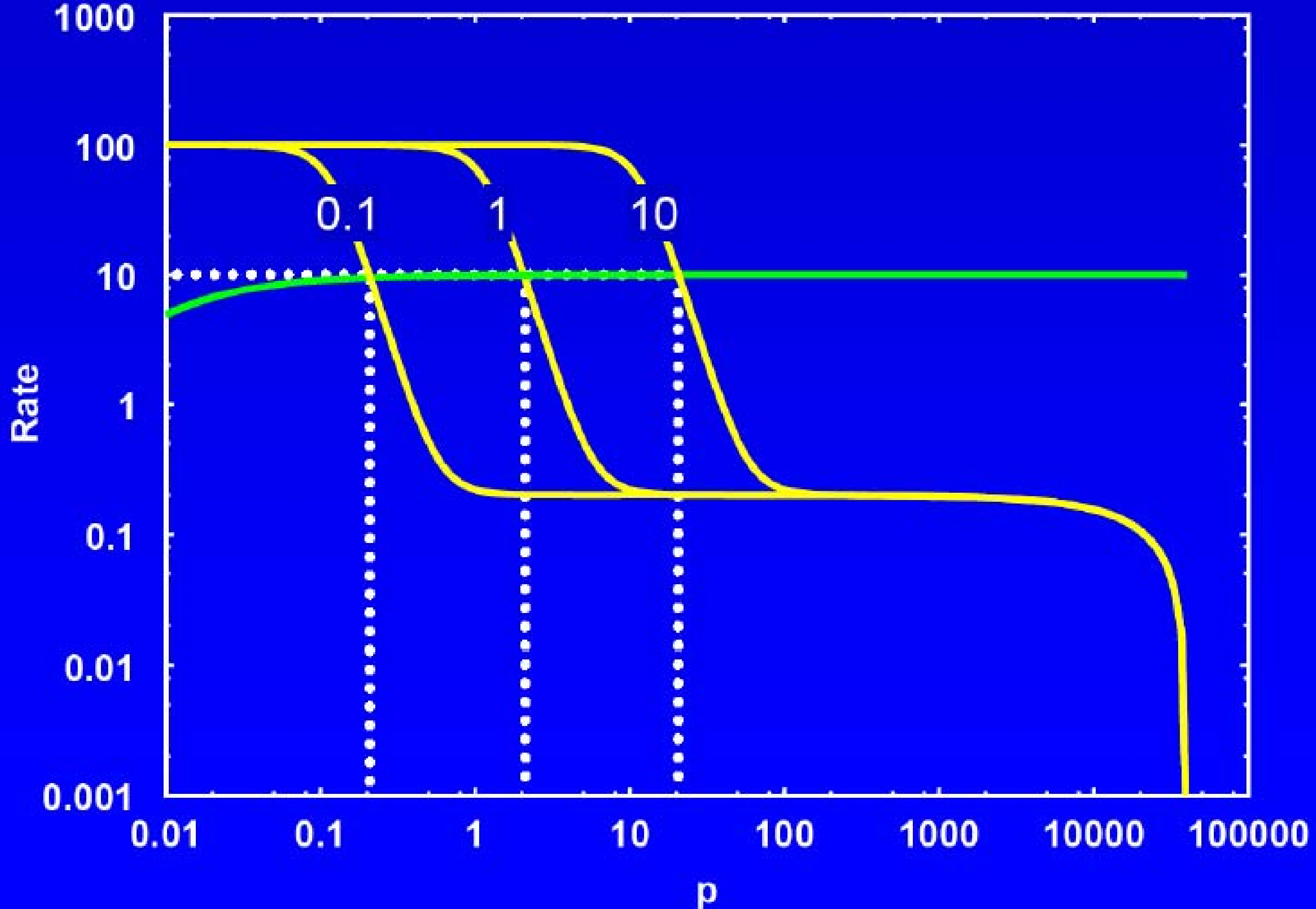
Reversible Hill equation with allosteric modifier

(Hofmeyr & Cornish-Bowden, 1997)

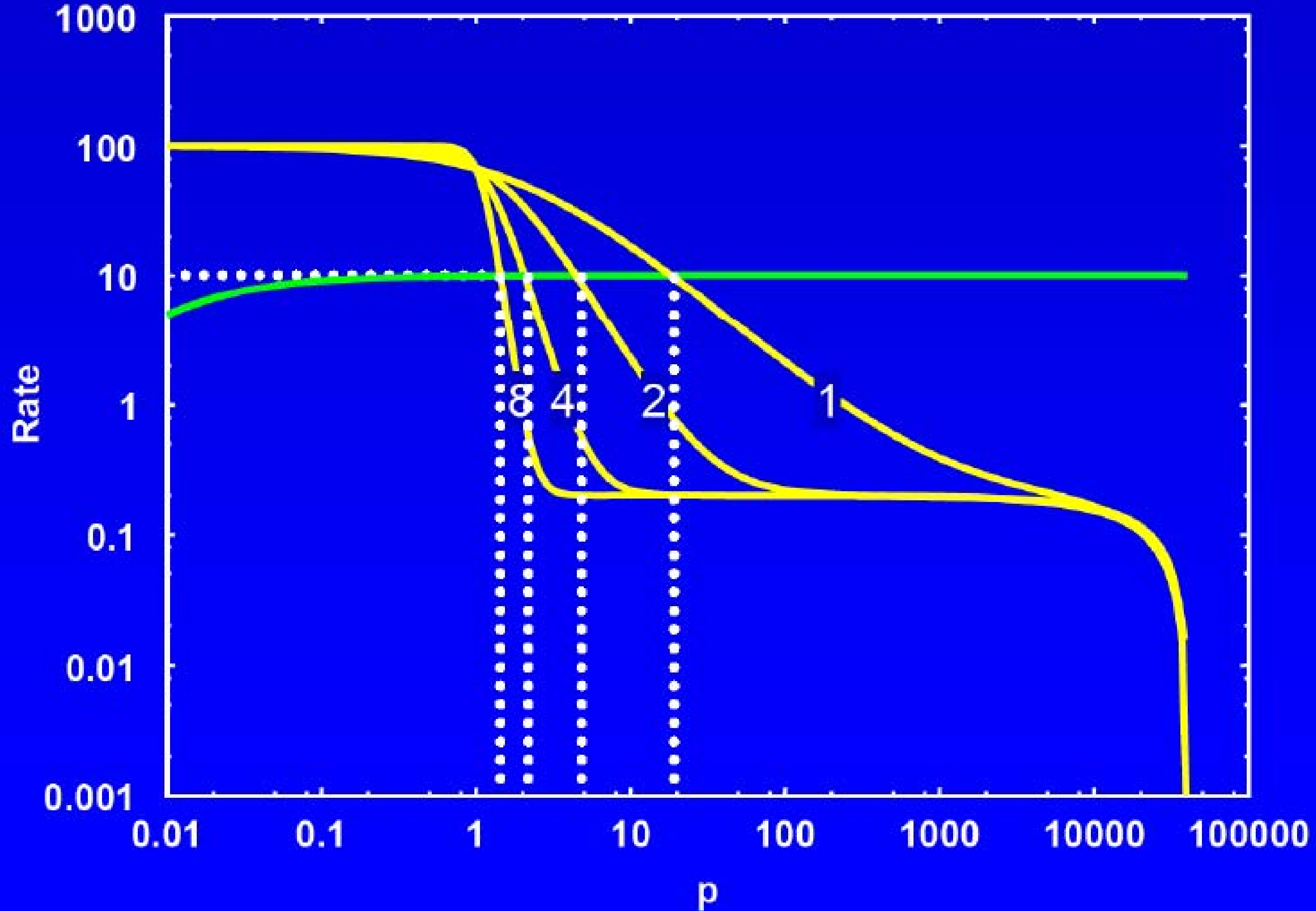
$$v = \frac{k_{cat}}{s_{0.5}} \cdot e_1 \cdot \frac{\left(\frac{s}{s_{0.5}} + \frac{a}{a_{0.5}}\right)^{h-1}}{\left(\frac{s}{s_{0.5}} + \frac{a}{a_{0.5}}\right)^{h} + \frac{1+\left(\frac{p}{p_{0.5}}\right)^{h}}{1+\alpha\left(\frac{p}{p_{0.5}}\right)^{h}}} \cdot \left(s - \frac{a}{K_{eq}}\right)$$


S
1
A
2
B
3
P
Demand
⊖
Rate characteristics
of supply and demand
Supply
or
demand
flux
10^2
10^1
10^0
10^{-1}
10^{-2}
10^{-2}
10^{-1}
10^0
10^1
10^2
10^3
10^4
p

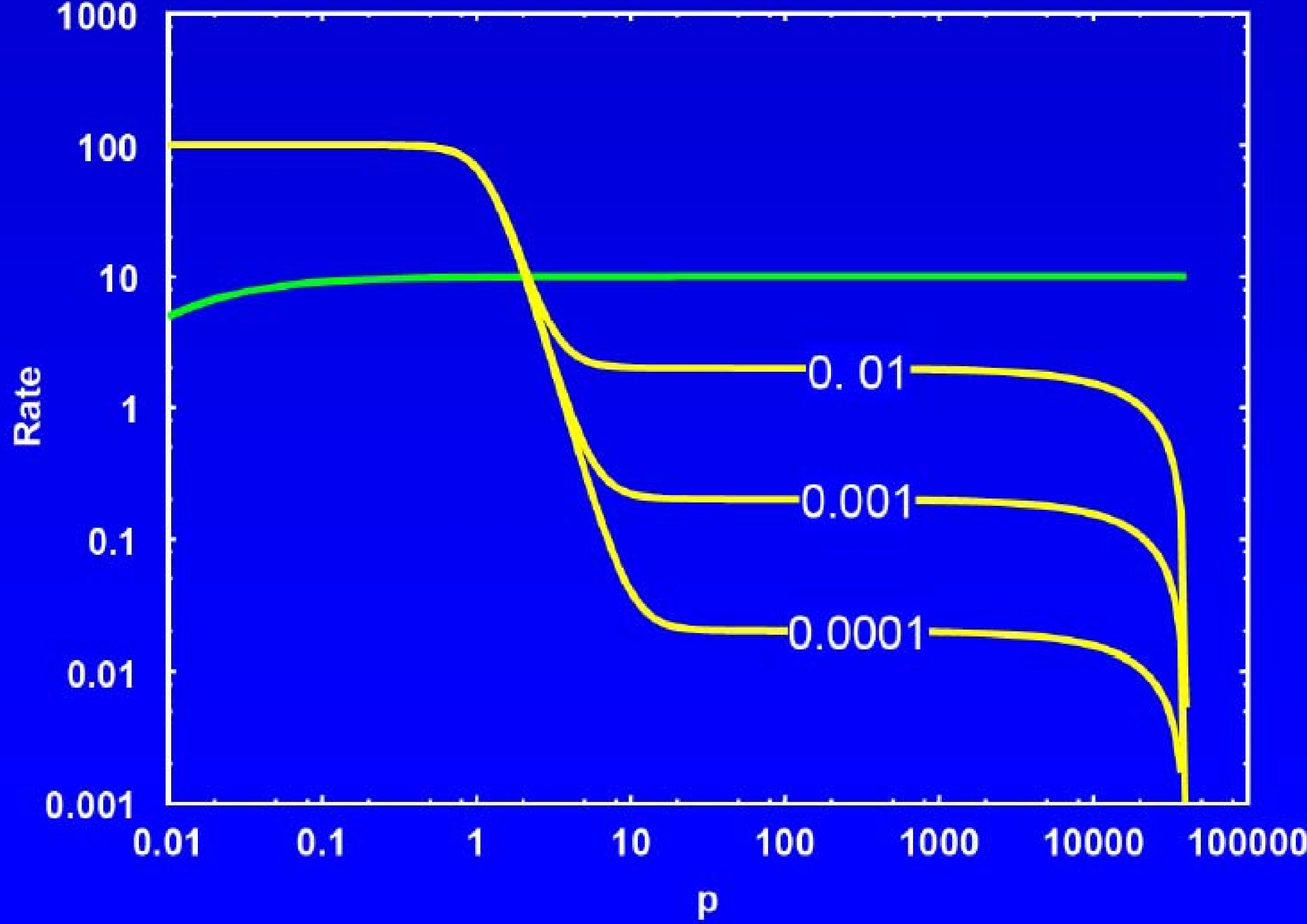
Varying the binding strength ($p_{0.5}$) of allosteric effector P



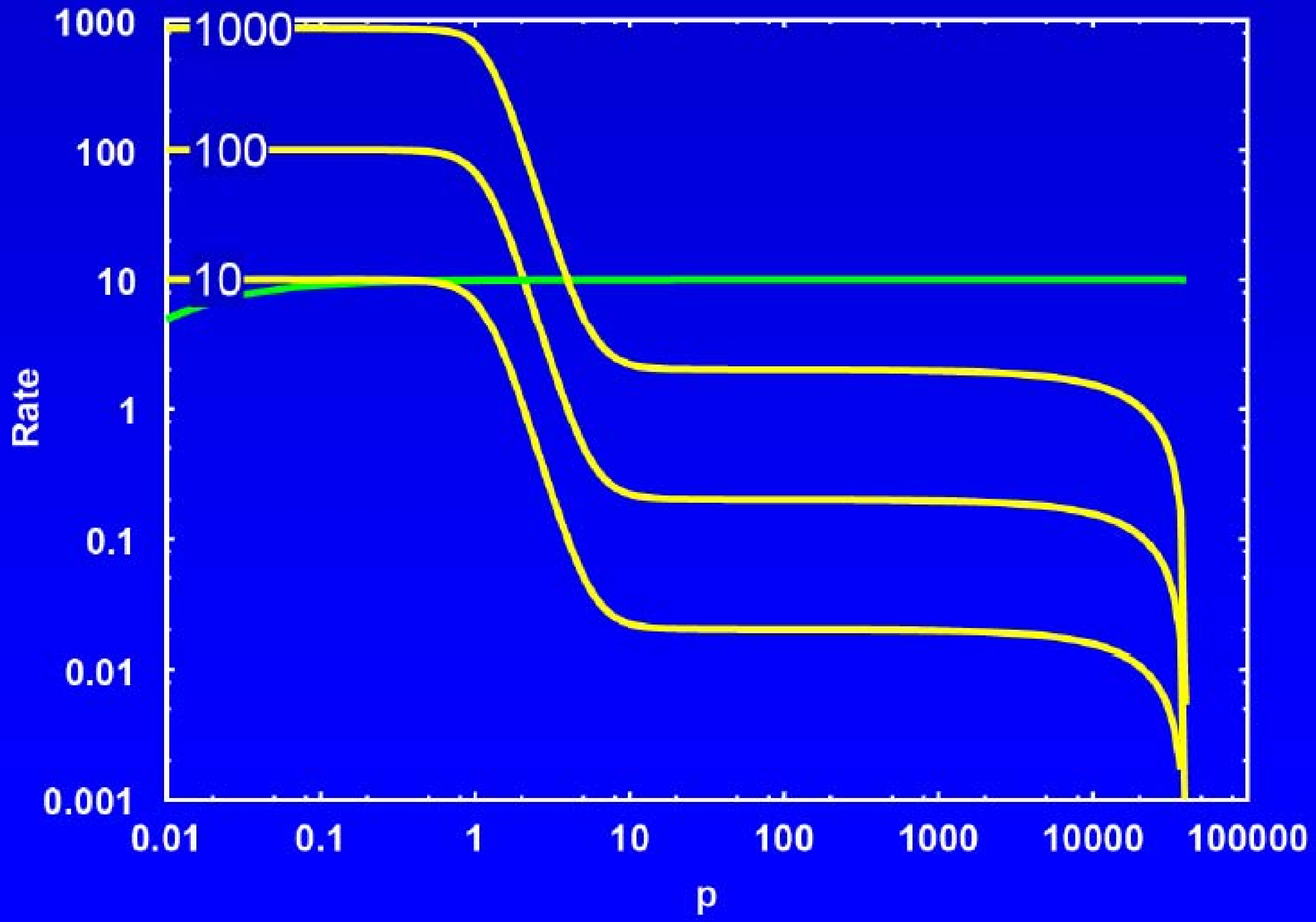
Varying the degree of cooperativity (*h*)

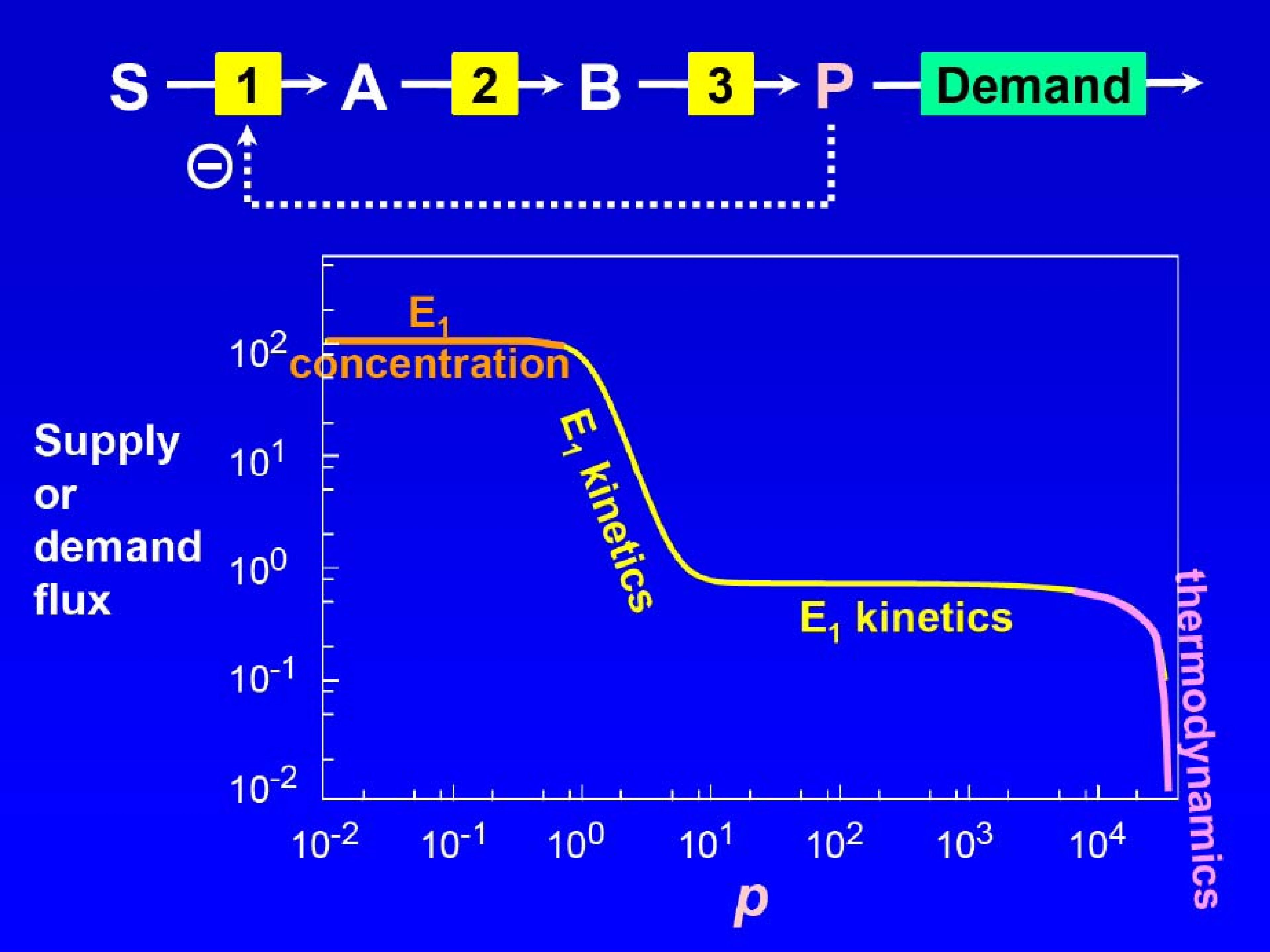


Varying the strength of allosteric inhibition of supply by P (α)

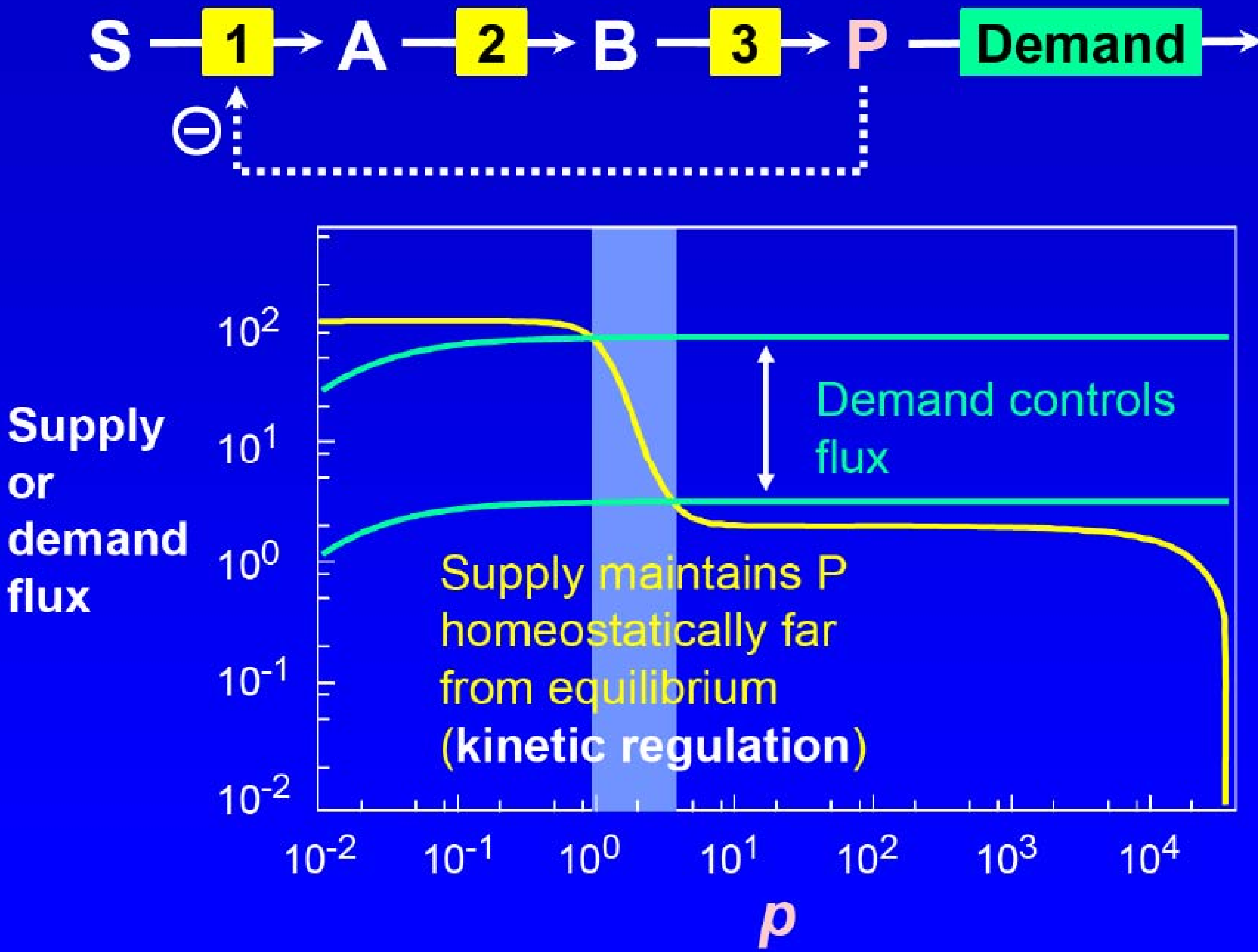


Varying the maximal capacity (V_{max}) of the supply through [E_1]

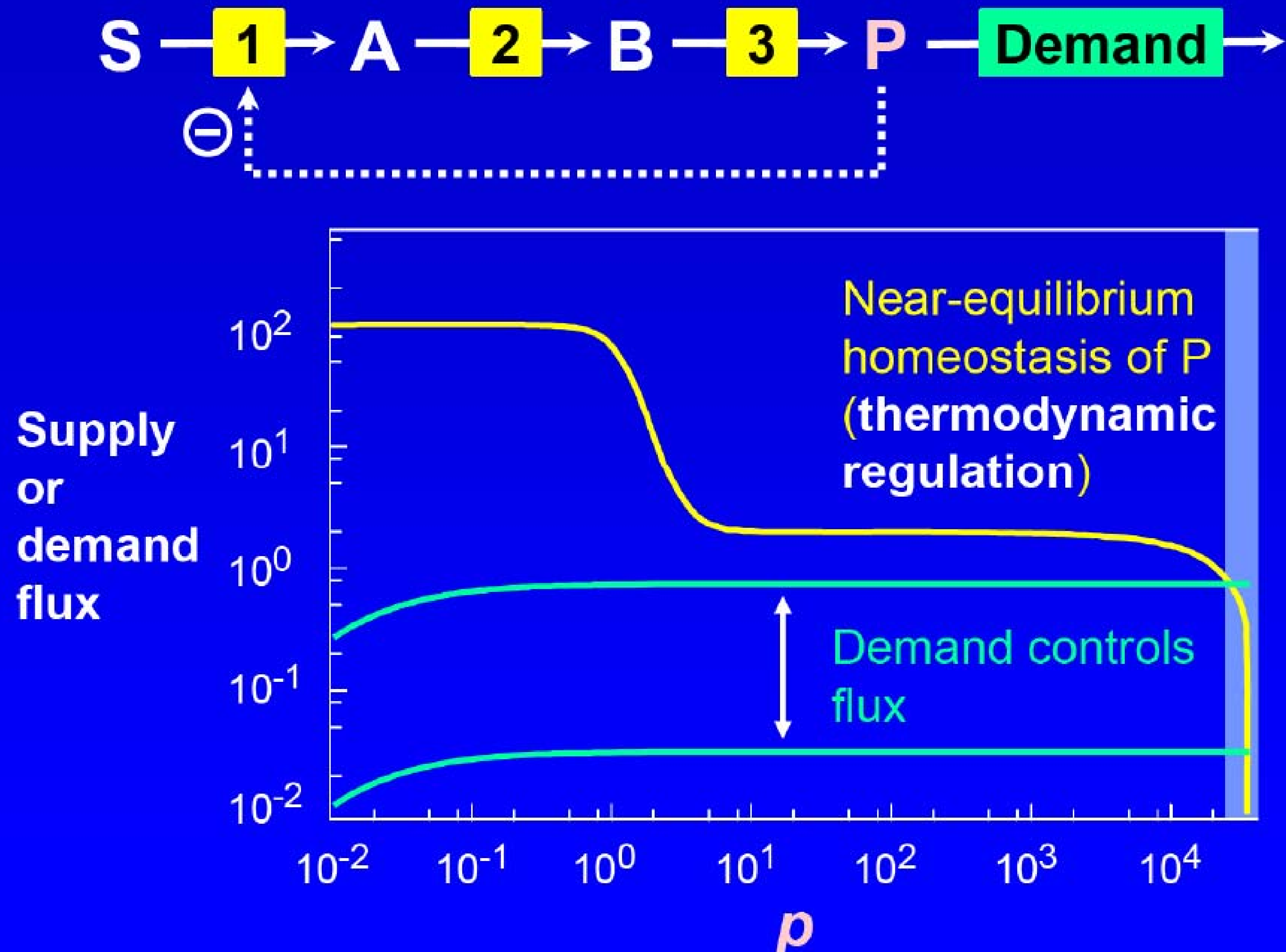


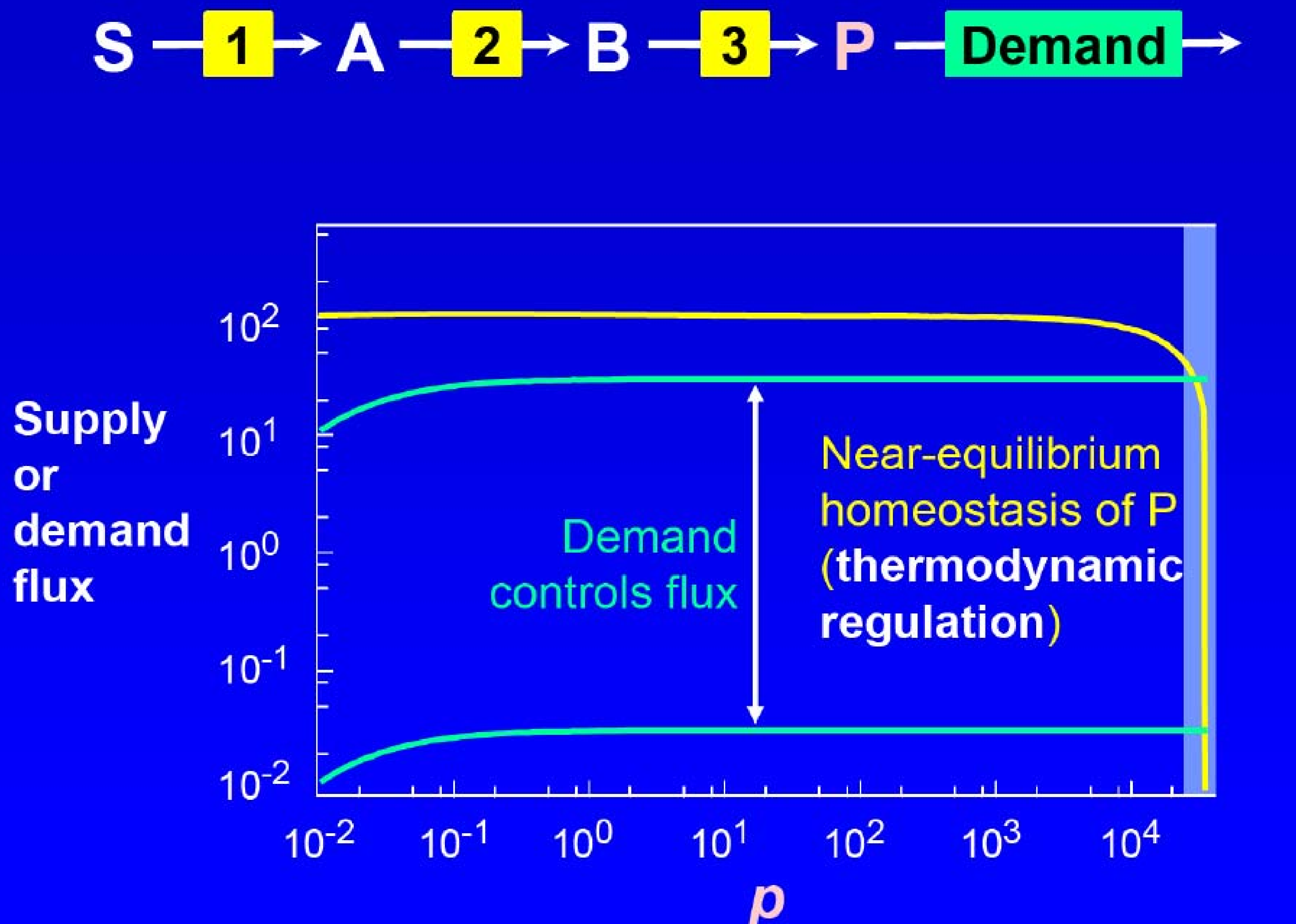


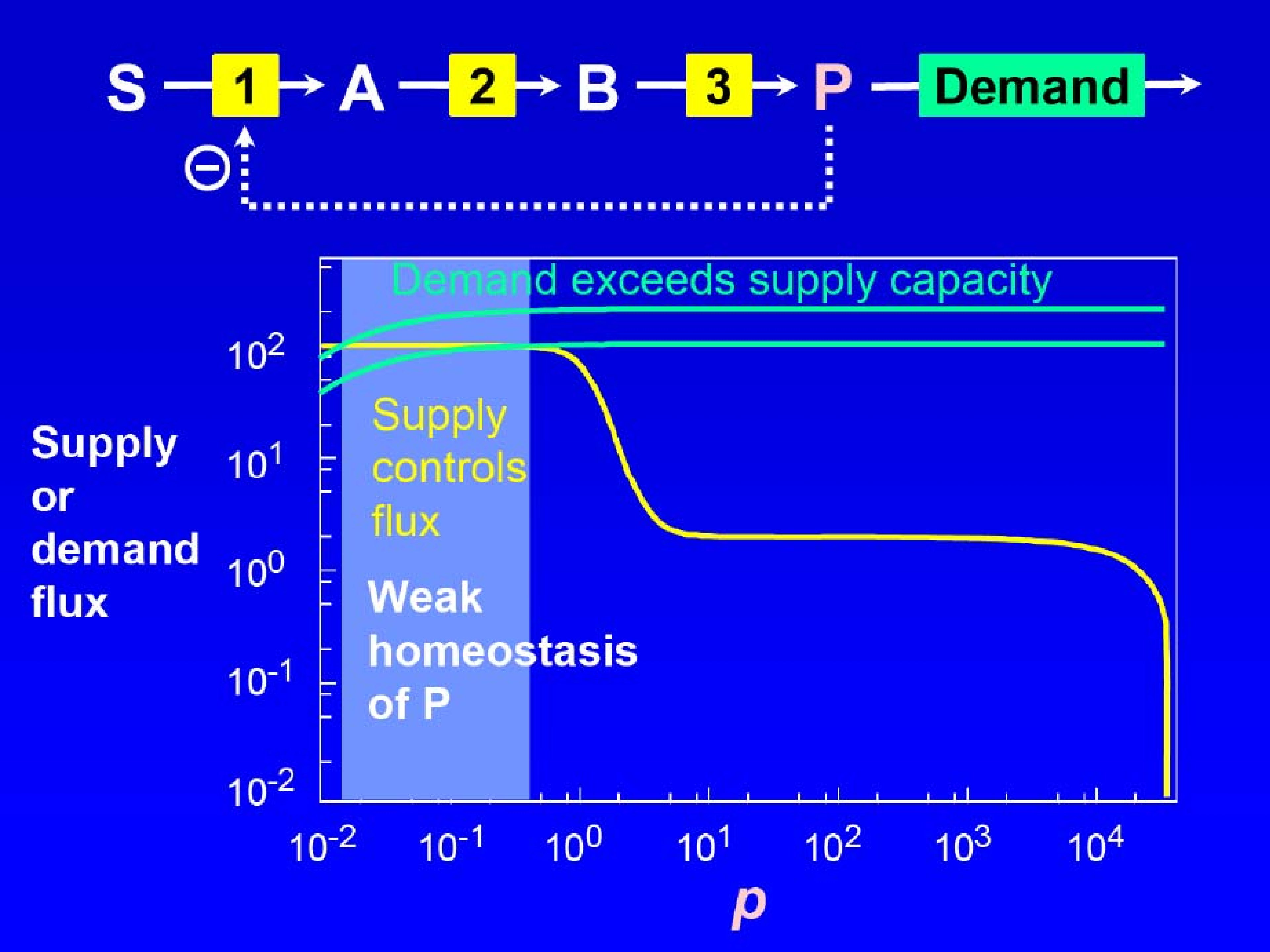
S
1
A
2
B
3
P
Demand
⊖
Supply or demand flux
10^2
10^1
10^0
10^{-1}
10^{-2}
E_1 concentration
E_1 kinetics
E_1 kinetics
thermodynamics
10^{-2}
10^{-1}
10^0
10^1
10^2
10^3
10^4
p



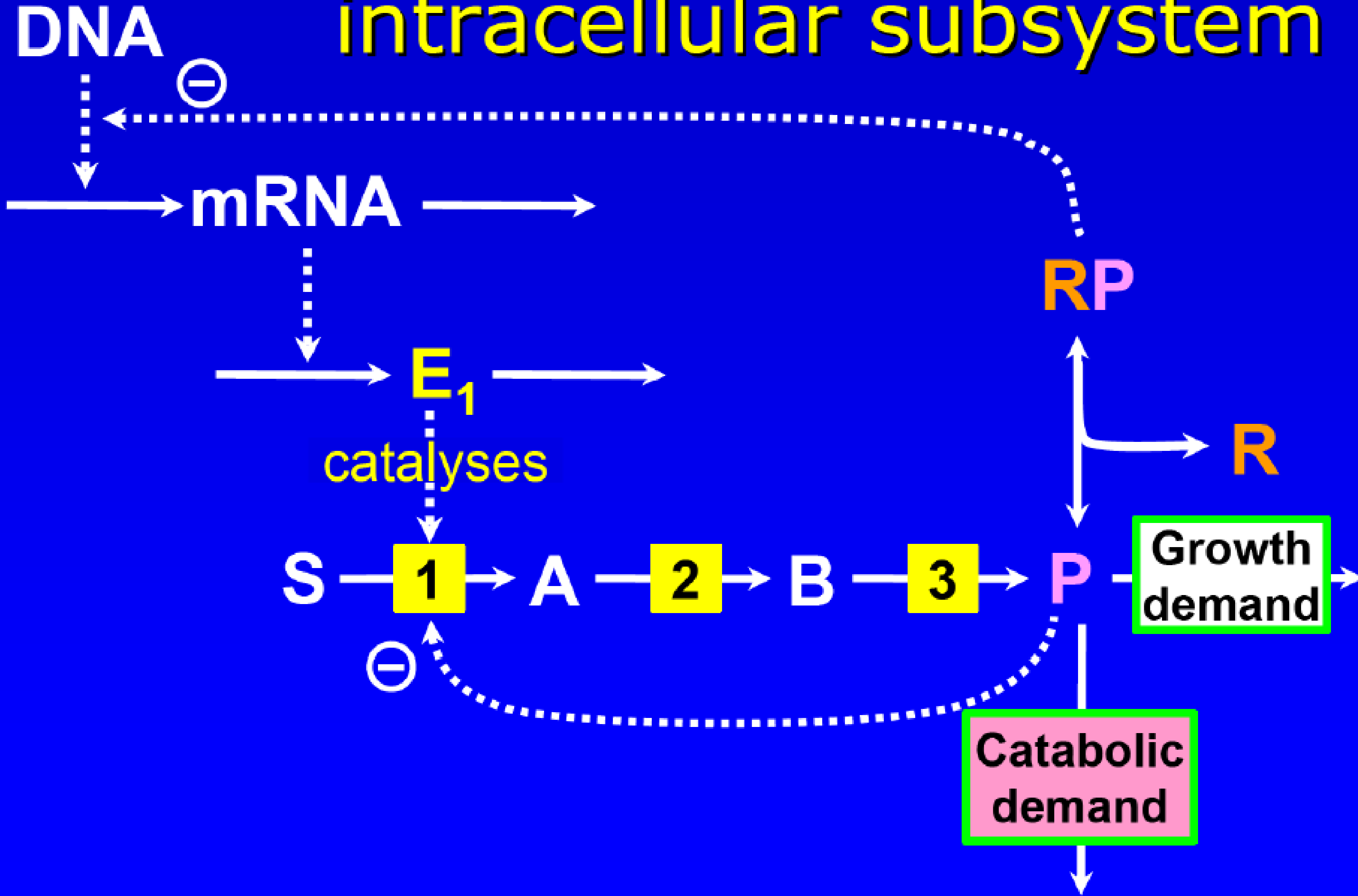
S
1
A
2
B
3
P
Demand
⊖
Supply or demand flux
10^2
10^1
10^0
10^{-1}
10^{-2}
Demand controls flux
Supply maintains P homeostatically far from equilibrium
(kinetic regulation)
10^{-2}
10^{-1}
10^0
10^1
10^2
10^3
10^4
p


S
1
A
2
B
3
P
Demand
⊖
Supply or demand flux
10^2
10^1
10^0
10^{-1}
10^{-2}
Near-equilibrium homeostasis of P (thermodynamic regulation)
Demand controls flux
10^{-2} 10^{-1} 10^0 10^1 10^2 10^3 10^4
p

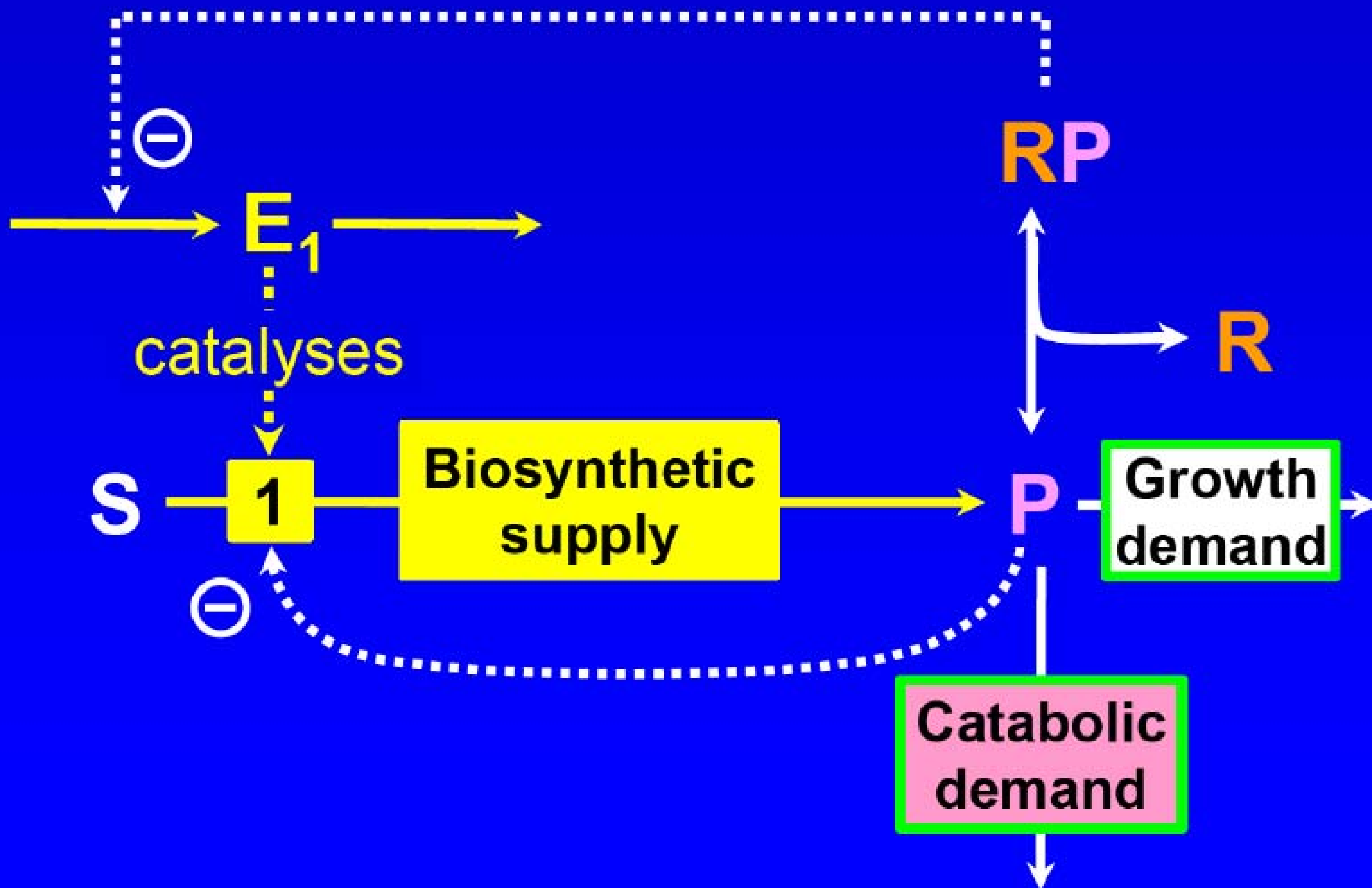

S
1
A
2
B
3
P
Demand
Supply or demand flux
Demand controls flux
Near-equilibrium homeostasis of P (thermodynamic regulation)
10^2
10^1
10^0
10^-1
10^-2
10^-2 10^-1 10^0 10^1 10^2 10^3 10^4
p

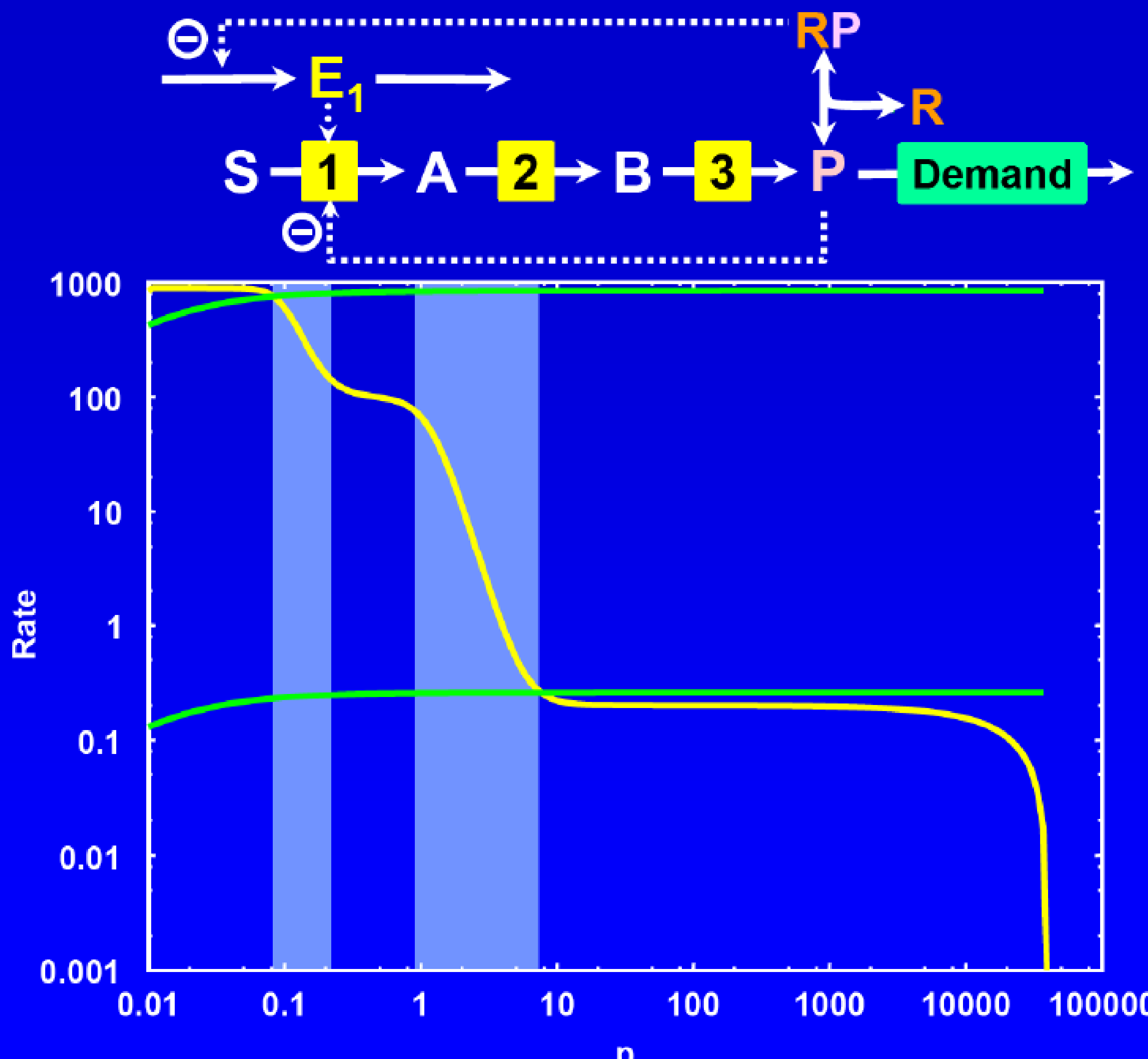

S
1
A
2
B
3
P
Demand
⊖
Demand exceeds supply capacity
Supply or demand flux
10^{2}
10^{1}
10^{0}
10^{-1}
10^{-2}
Supply controls flux
Weak homeostasis of P
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
10^{4}
p

A typical regulated intracellular subsystem



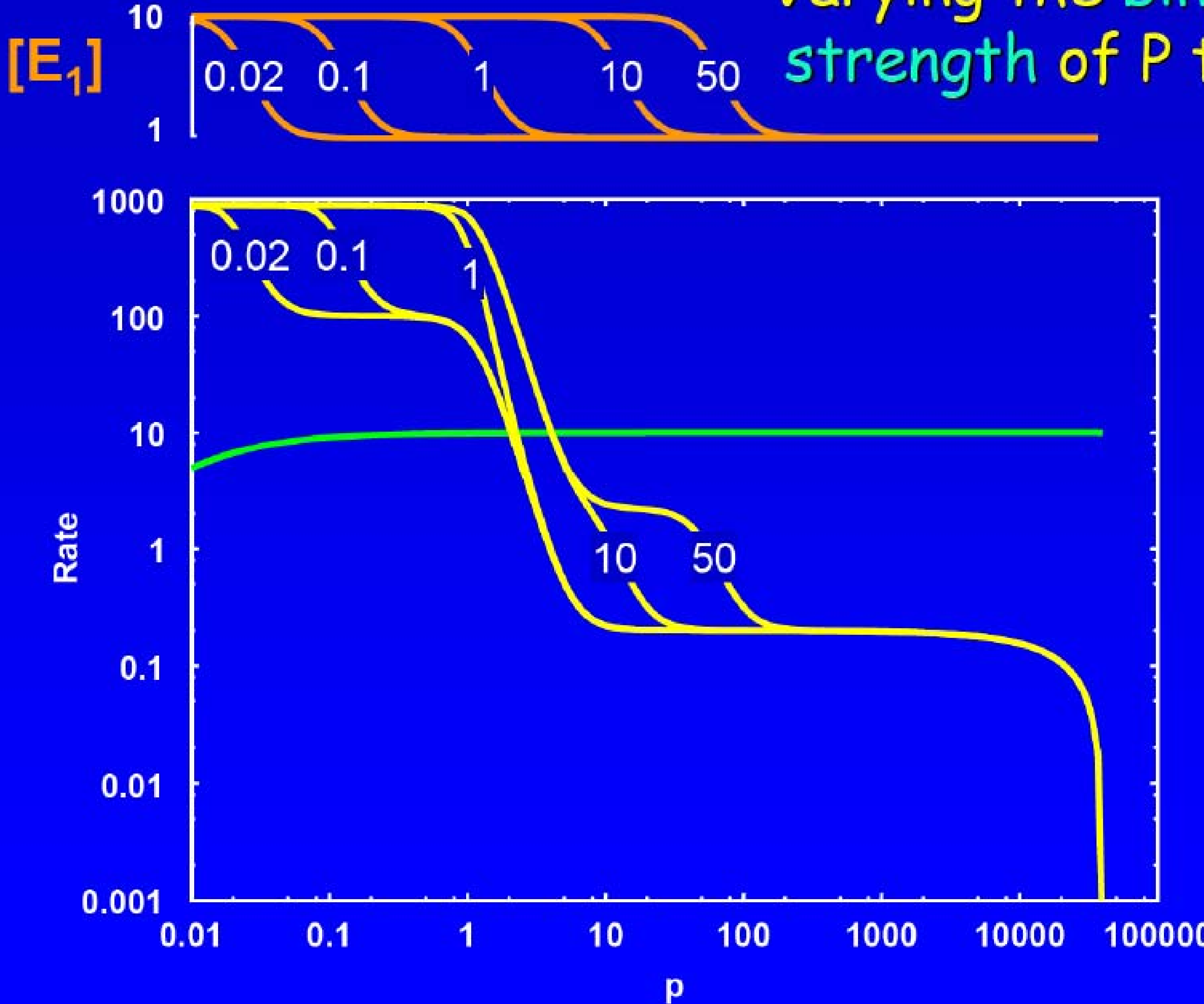
Simplified core model

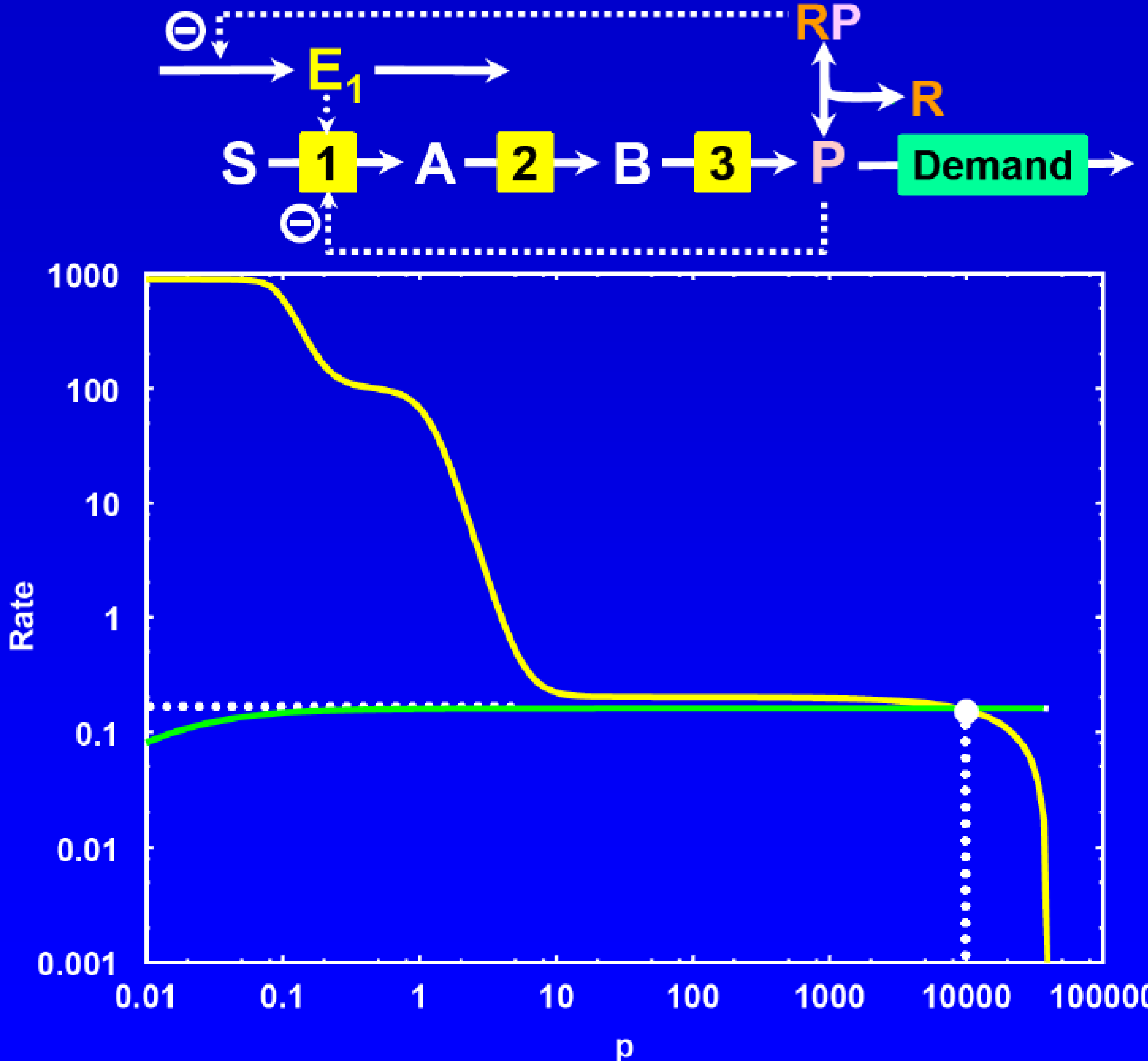




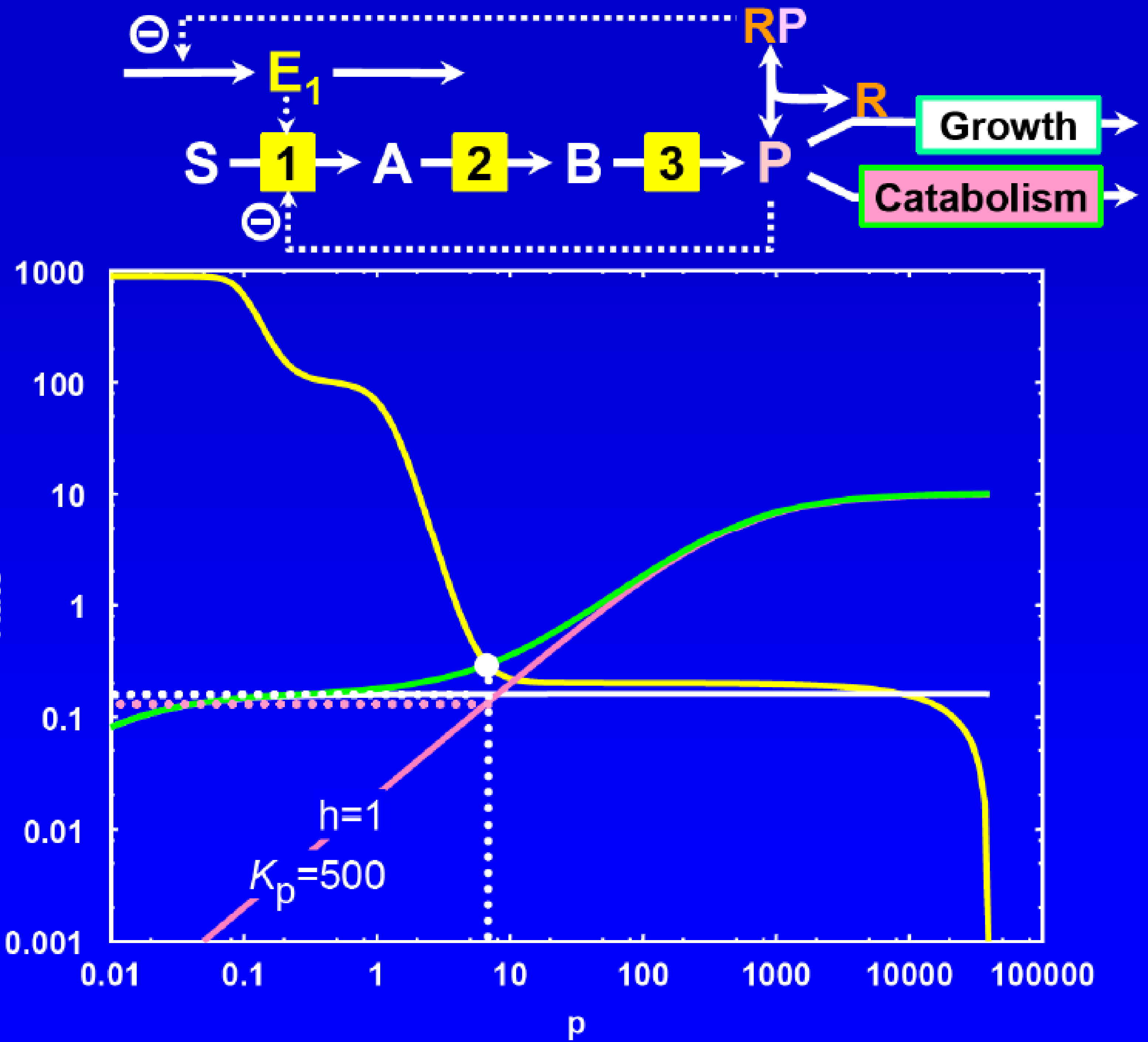
RP
E1
R
S
1
A
2
B
3
P
Demand
1000
100
10
1
0.1
0.01
0.001
Rate
0.01
0.1
1
10
100
1000
10000
100000
p

Varying the binding strength of P to R

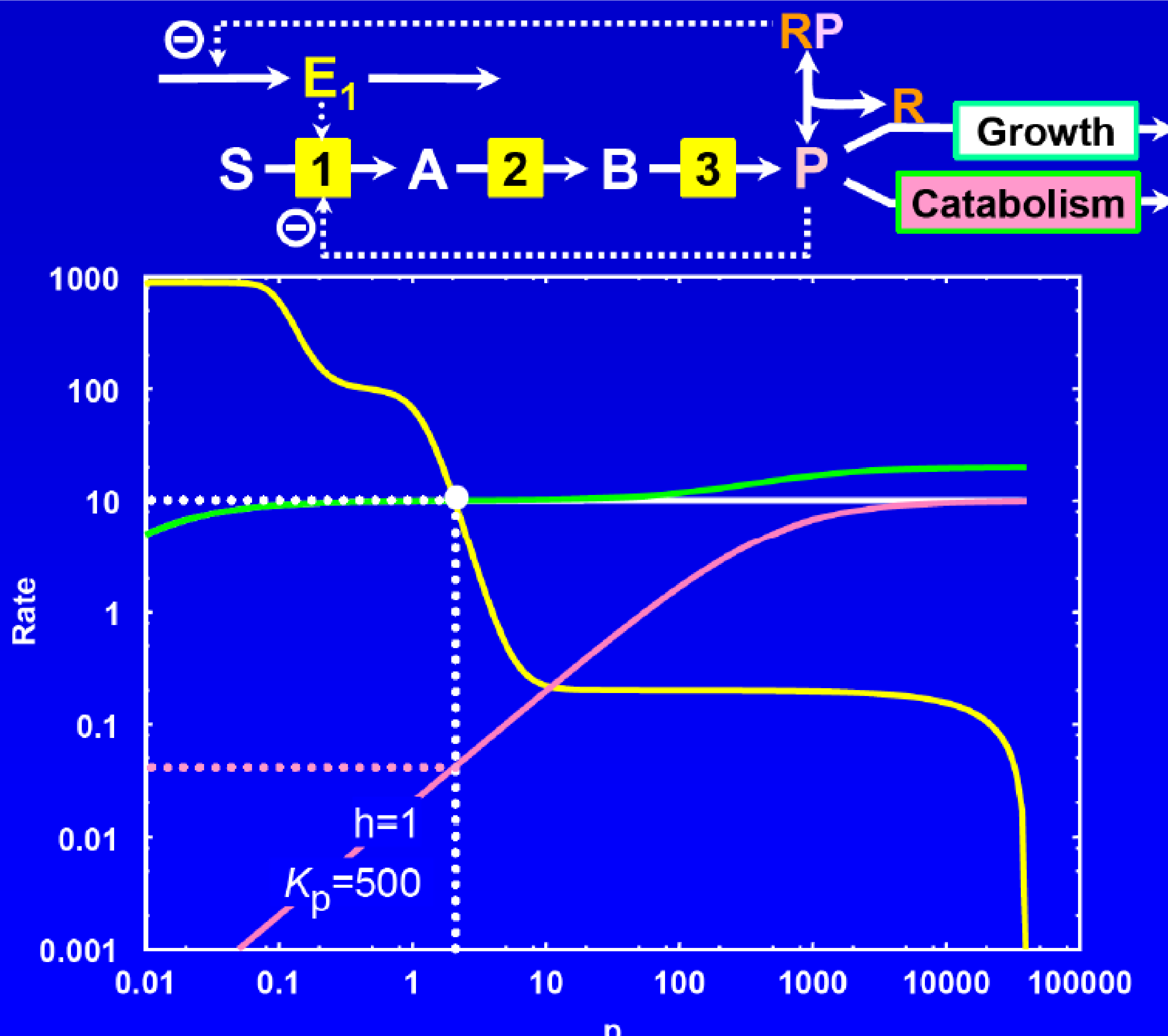




RP
E1
R
S
1
A
2
B
3
P
Demand
1000
100
10
1
0.1
0.01
0.001
Rate
0.01
0.1
1
10
100
1000
10000
100000
p



E1
RP
R
S
1
A
2
B
3
P
Growth
Catabolism
1000
100
10
1
0.1
0.01
0.001
Rate
h=1
Kp=500
0.01
0.1
1
10
100
1000
10000
100000
p


RP
E1
R
Growth
S
1
A
2
B
3
P
Catabolism
1000
100
10
1
0.1
0.01
0.001
Rate
h=1
Kp=500
0.01
0.1
1
10
100
1000
10000
100000
p