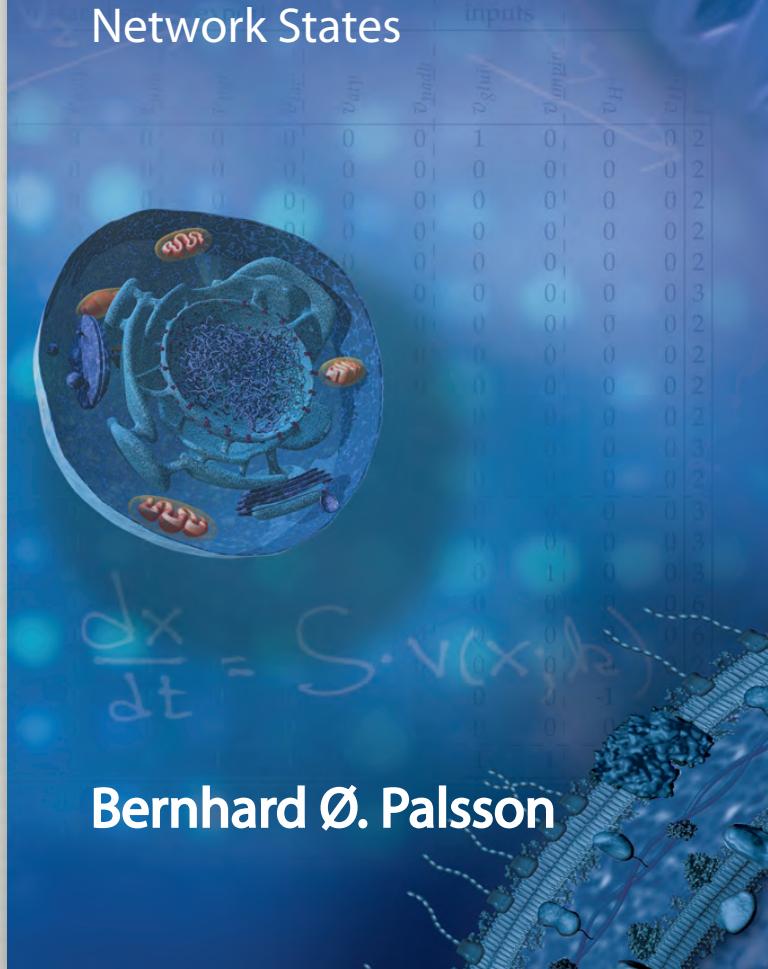


Systems Biology

Simulation of Dynamic Network States

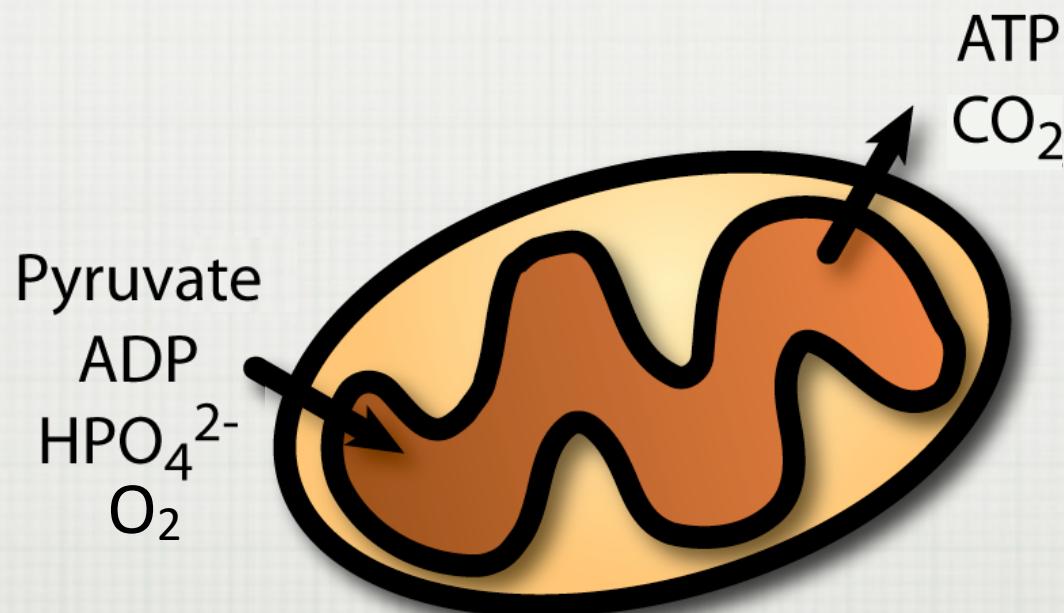


Lecture #6

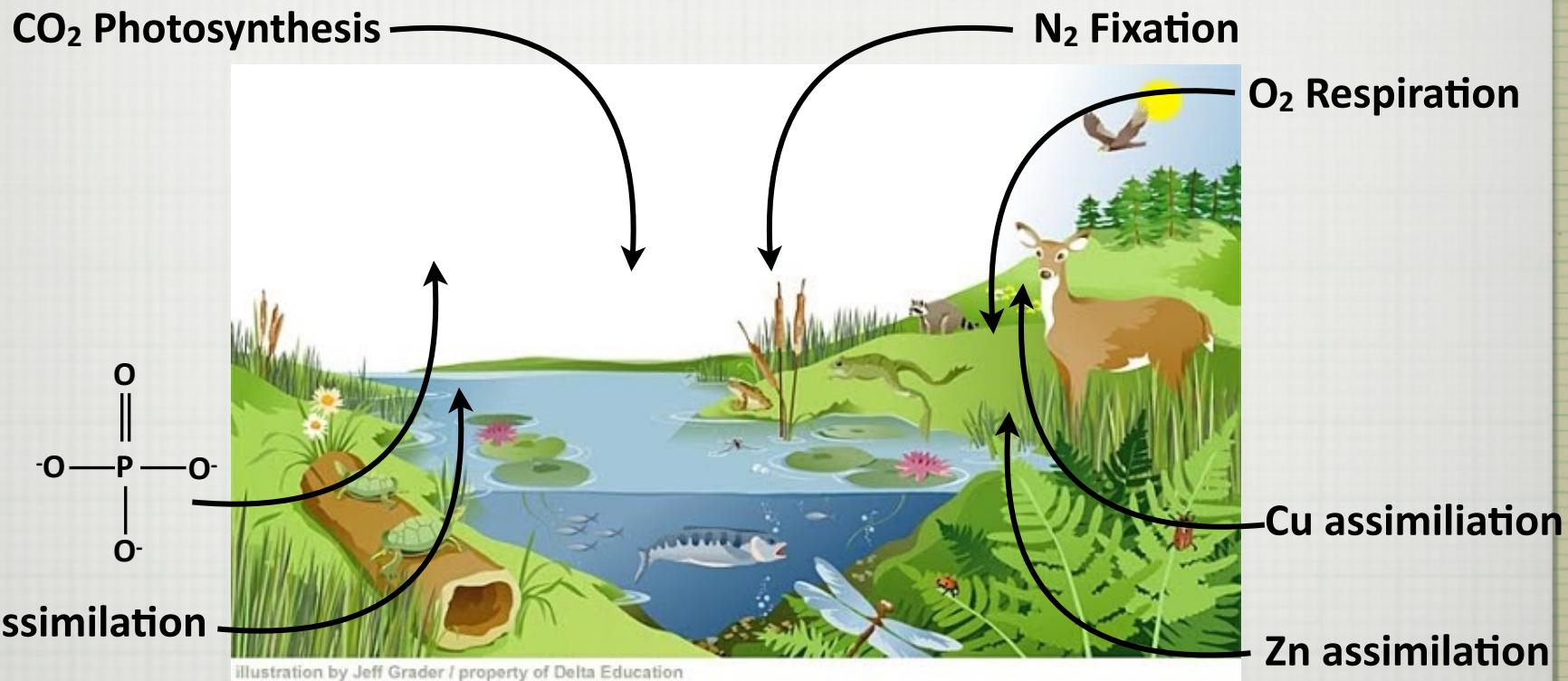
Open Systems

Biological systems are ‘open:’

Example: ATP production by mitochondria



Global interaction of the biotic and a biotic world



The most challenging processes in biology involve interactions with the abiotic world

Outline

- Key concepts in the analysis of open systems
- The reversible reaction in an open environment
- The Michaelis-Menten reaction mechanism in an open environment
- Lessons learned

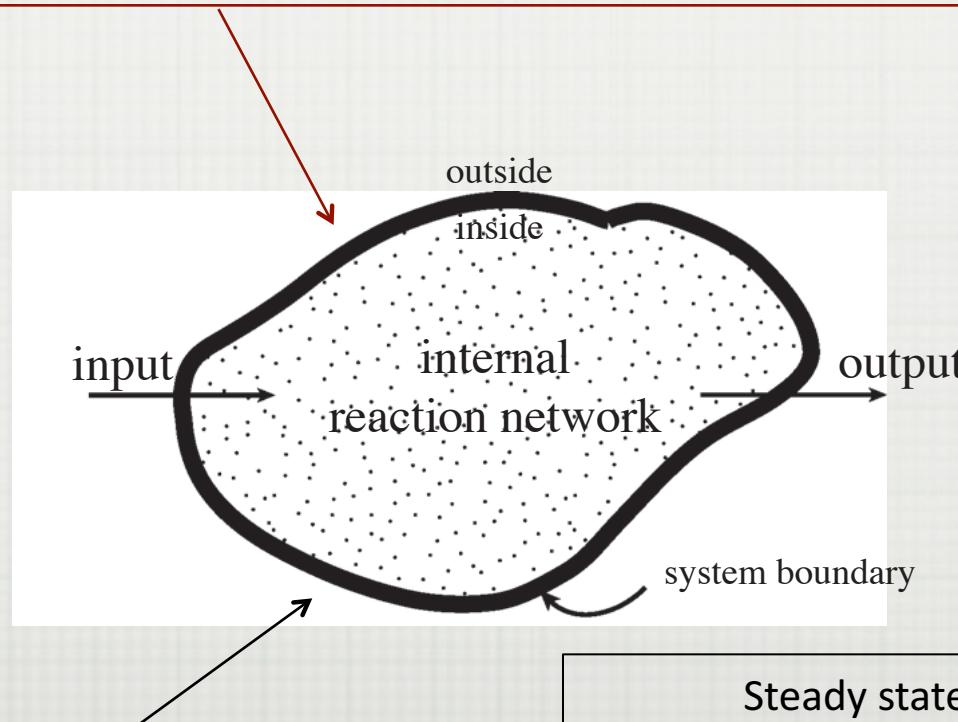
Key Concepts

- Systems boundary
 - inside vs. outside
- Crossing the boundary
 - I/O
- Inside the boundary:
 - the internal network;
 - hard to observe directly (i.e., non-invasively)
- Computing functional states
 - Steady states → homeostatic states
 - Dynamic states → transition from one steady state to another

Open Systems: key concepts

Physical: i.e., cell wall, nuclear membrane

Virtual: i.e., the amino acid biosynthetic pathways



Hard: volume = constant

Soft: volume = $f_n(\text{time})$

Steady state/homeostasis
<https://en.wikipedia.org/wiki/Homeostasis>

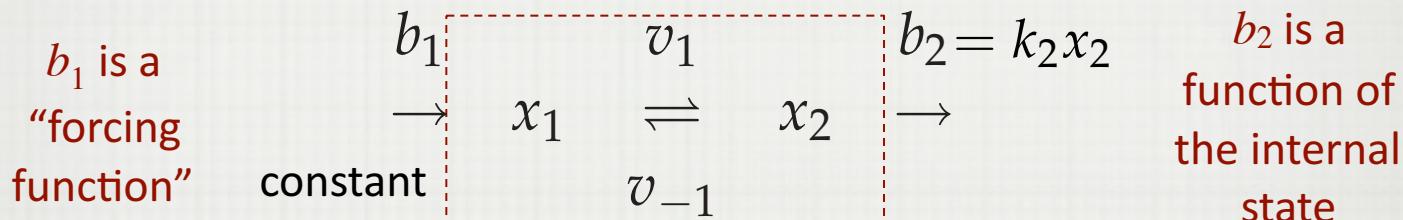
← recall assumptions from chapter 2

Start simple

THE REVERSIBLE REACTION IN AN OPEN SETTING

The reversible reaction

The basic equations

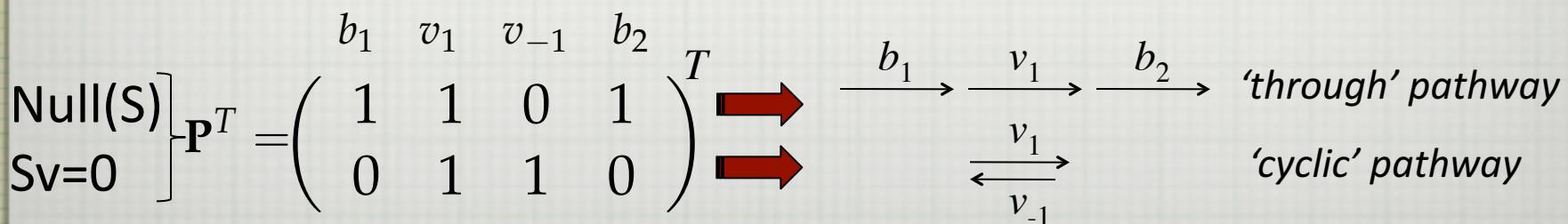


$$\mathbf{S} = \begin{pmatrix} b_1 & v_1 & v_{-1} & b_2 \\ 1 & -1 & 1 & 0 \\ 0 & 1 & -1 & -1 \end{pmatrix} \begin{matrix} x_1 \\ x_2 \end{matrix}$$

$$m = 2, n = 4, r = 2$$

$$\text{Dim(Null)} = 4-2=2$$

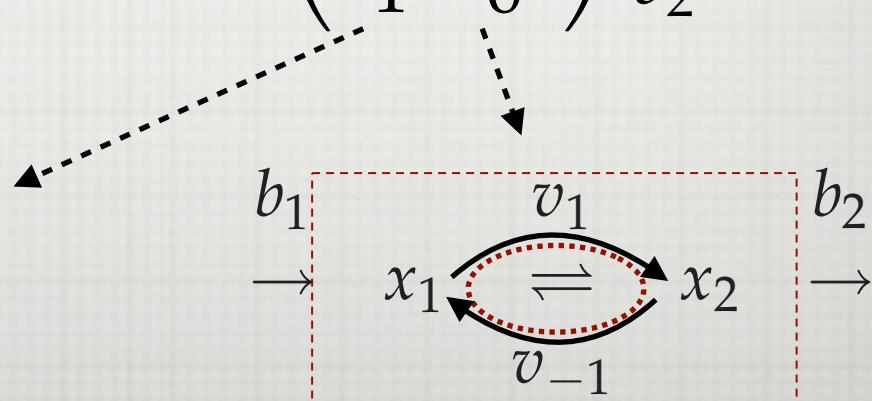
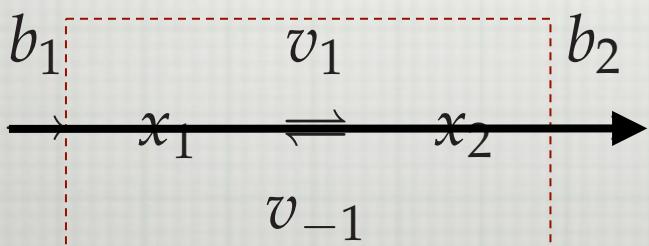
$$\text{Dim(L.Null)}=2-2=0$$



Visualization of pathway vectors

$$\mathbf{S} \cdot \mathbf{P} = 0$$

$$\mathbf{S} = \begin{pmatrix} b_1 & v_1 & v_{-1} & b_2 \\ 1 & -1 & 1 & 0 \\ 0 & 1 & -1 & -1 \end{pmatrix} \begin{pmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 1 & 0 \end{pmatrix} \begin{matrix} b_1 \\ v_1 \\ v_{-1} \\ b_2 \end{matrix}$$



The Steady State

Dynamic mass
balances

$$\frac{dx_1}{dt} = b_1 - k_1 x_1 + k_{-1} x_2 \quad (1)$$

$$\frac{dx_2}{dt} = k_1 x_1 - k_{-1} x_2 - k_2 x_2 \quad (2)$$

$$\frac{d\mathbf{x}}{dt} = 0 \longrightarrow \begin{cases} \mathbf{x}_{ss} = (x_{1,ss}, x_{2,ss}) \\ = \left(\frac{b_1}{k_1} \left[1 + \frac{k_{-1}}{k_2} \right], \frac{b_1}{k_2} \right) \end{cases}$$

Some details:

$$\text{From (1)} \quad b_1 = k_1 x_1 - k_{-1} x_2$$

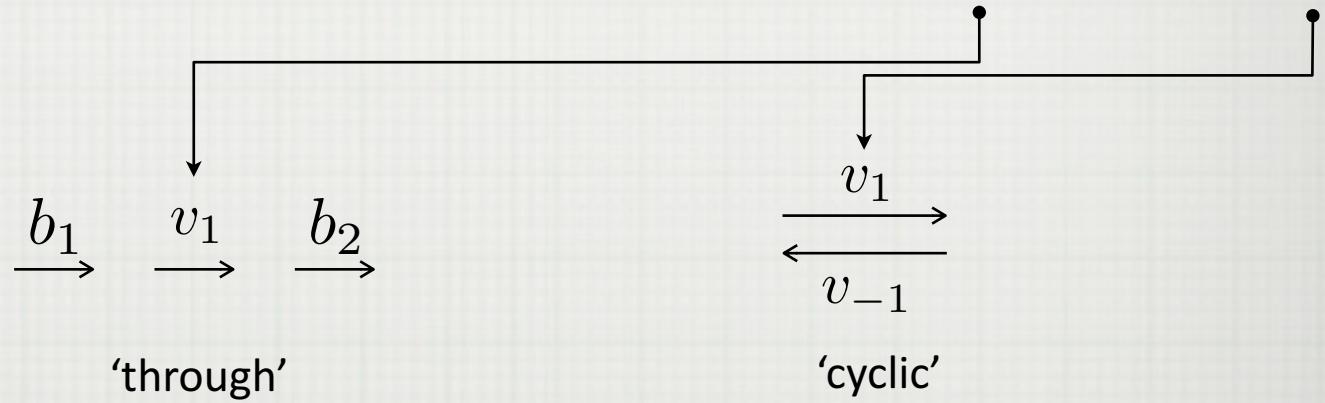
$$\text{From (2)} \quad k_1 x_1 - k_{-1} x_2 = k_2 x_2$$

$$b_1 = k_2 x_2 \rightarrow x_{2,ss} = \underbrace{\frac{b_1}{k_2}}$$

$$k_1 x_1 - (k_{-1} + k_2) x_2 \xrightarrow{\text{substitute into (2)}} x_{1,ss} = \frac{(k_{-1} + k_2)}{k_1} x_{2,ss} = \frac{b_1}{k_1} \left[1 + \frac{k_{-1}}{k_2} \right]$$

The Steady State Flux Vector

$$\mathbf{v}_{ss} = \begin{pmatrix} b_1 \\ v_1 \\ v_{-1} \\ b_2 \end{pmatrix} = \begin{pmatrix} b_1 \\ k_1 x_{1,ss} \\ k_{-1} x_{2,ss} \\ k_2 x_{2,ss} \end{pmatrix} = \begin{pmatrix} b_1 \left[1 + \frac{k_{-1}}{k_2} \right] \\ b_1 \frac{k_{-1}}{k_2} \\ b_1 \end{pmatrix} = b_1 \begin{pmatrix} 1 \\ 1 \\ 0 \\ 1 \end{pmatrix} + \frac{b_1 k_{-1}}{k_2} \begin{pmatrix} 0 \\ 1 \\ 1 \\ 0 \end{pmatrix}$$



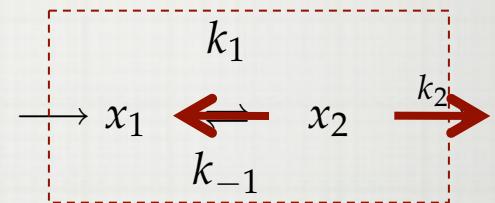
NOTES

- (1) the flux through the ‘cyclic’ pathway is (k_{-1}/k_2) times the flux in the ‘through’ pathway
- (2) the entire flux map is proportional to the input flux, b_1

Analysis/Interpretation

The “Distance” from Equilibrium
the difference between life and death

$$\frac{\Gamma}{K_{eq}} = \frac{x_{2,ss}/x_{1,ss}}{x_{2,eq}/x_{1,eq}}$$



$$= \frac{1}{1+k_2/k_{-1}} \xrightarrow{k_2 \ll k_{-1}} 1$$

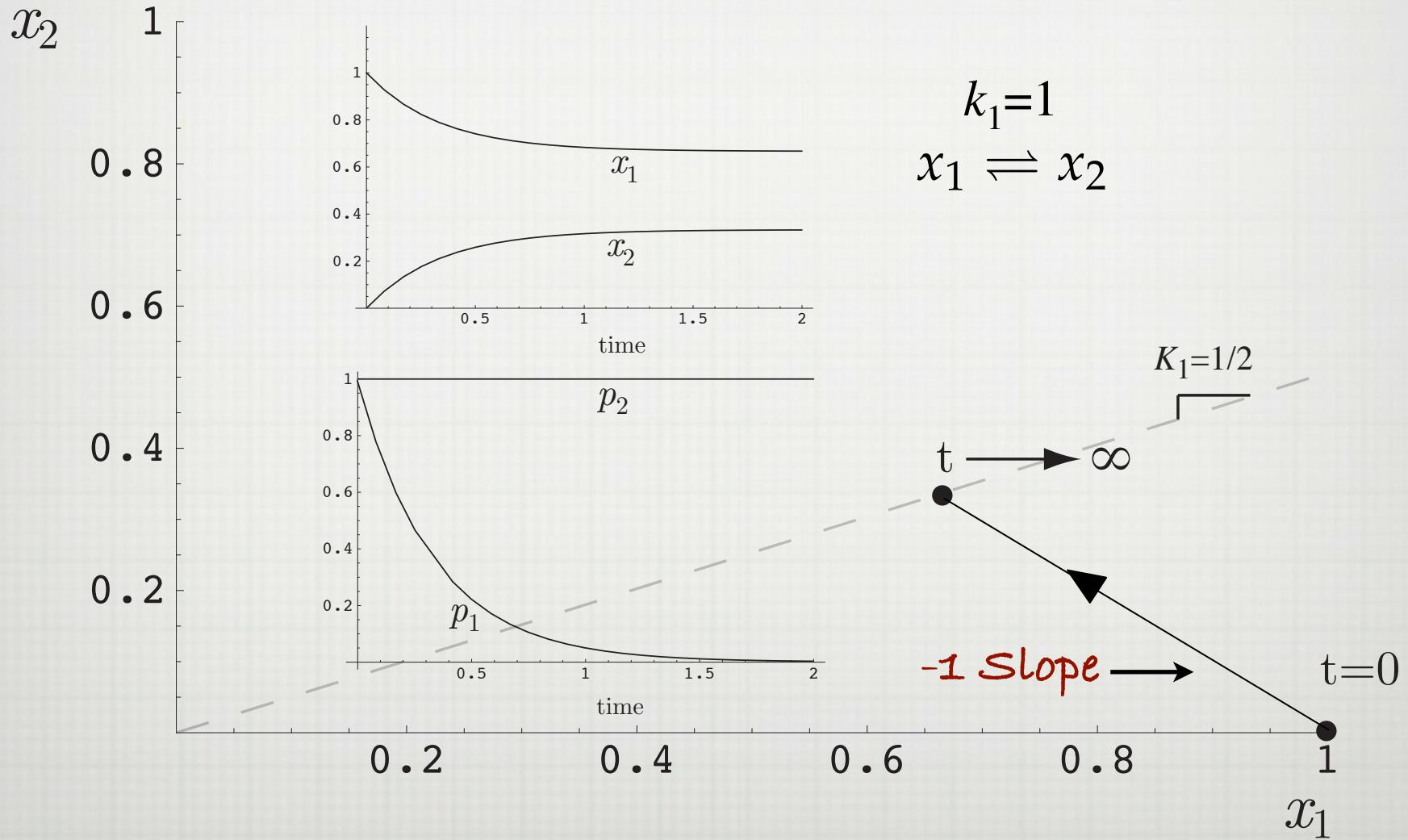
Γ : the mass action ratio

K_{eq} : the equilibrium constant

$\Gamma/K_{eq} < 1$ the reaction proceeds
in the forward direction

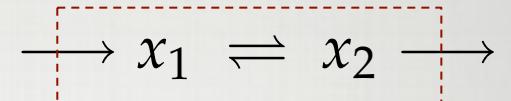
The Reversible Reaction:

recall the response in closed system from Ch 4



Dynamic Response of an Open System

$$(x_{1,0} = 1, x_{2,0} = 0)$$



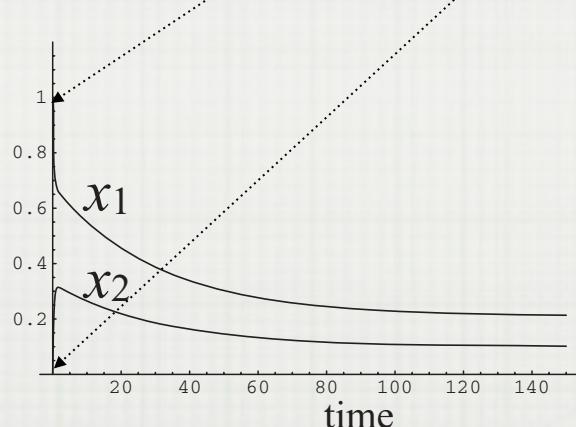
(a) x_2

0.5

(b)

0.4

0.3



$$\begin{aligned} \text{internal} & \left\{ \begin{array}{l} k_1 = 1 \\ k_{-1} = 2 \end{array} \right. \\ \text{external} & \left\{ \begin{array}{l} k_2 = 0.1 \\ b_1 = 0.01 \end{array} \right. \end{aligned}$$

$\frac{1}{2}$

← equilibrium line

motion of
a Qe state

motion towards
a Qe state

$x_{2,ss}$

0.2

0.1

$$= \left(\frac{b_1}{k_1} \left[1 + \frac{k_{-1}}{k_2} \right], \frac{b_1}{k_2} \right)$$

Can use analytical
solution as QC/QA test

0.2

$x_{1,ss}$

0.6

x_1

0.4

0.8

$t = 0$

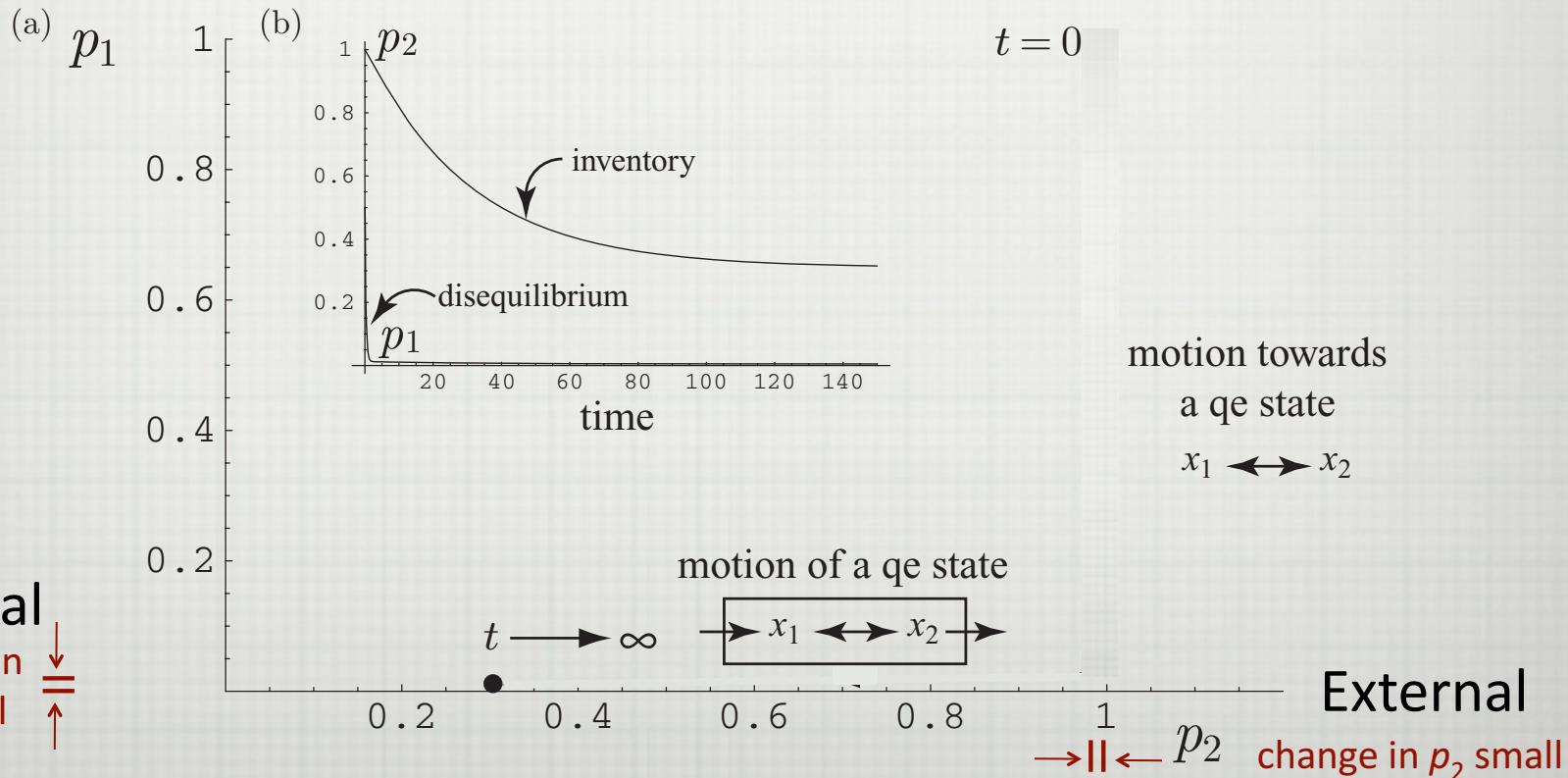
0.2

$t \rightarrow \infty$

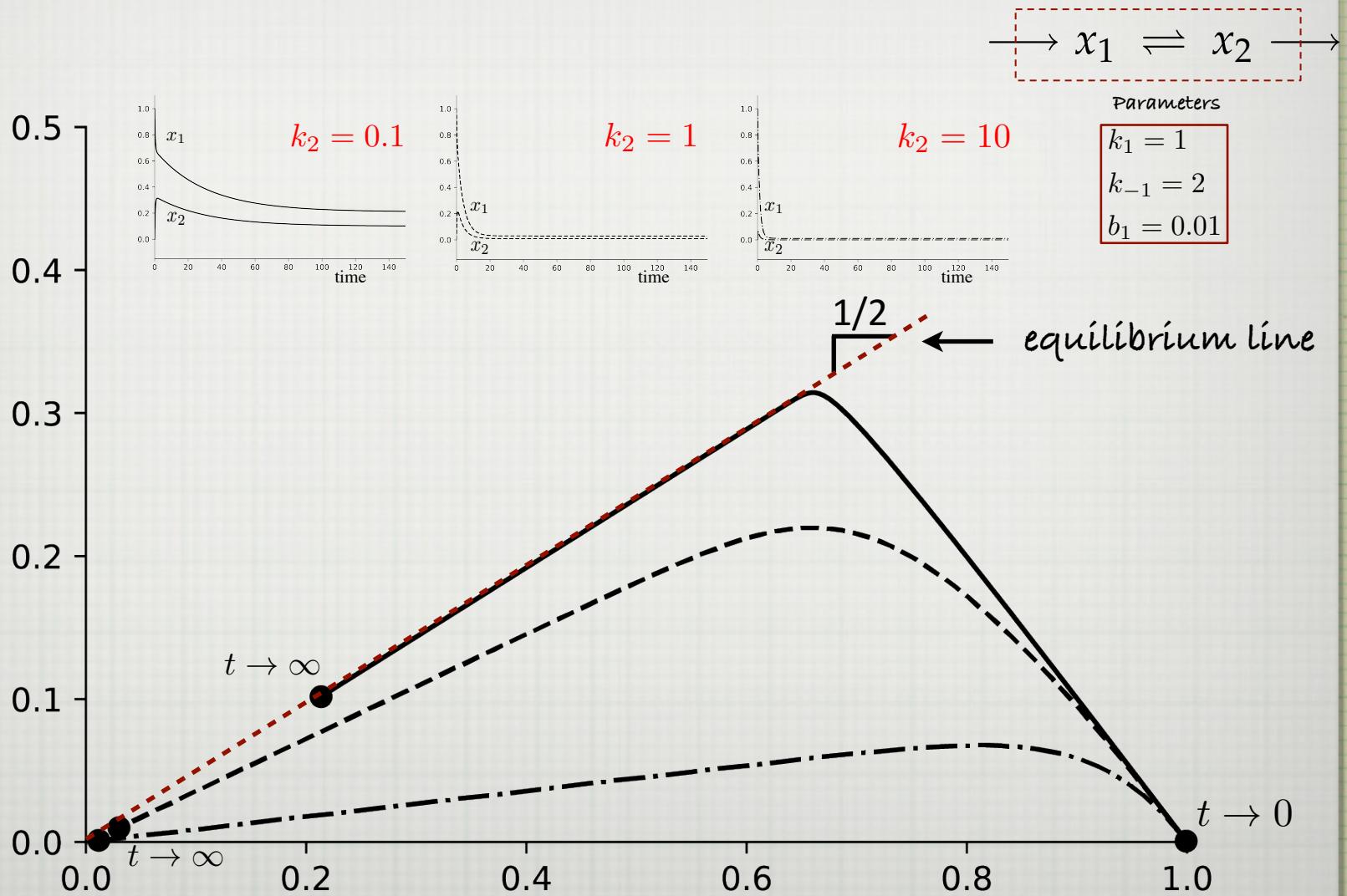
Dynamic Response of the Pools:

post-processing the solution

$$\begin{pmatrix} p_1 \\ p_2 \end{pmatrix} = \begin{pmatrix} 1 & -1/K_{eq} \\ 1 & 1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} x_1 - x_2/K_{eq} \\ x_1 + x_2 \end{pmatrix} \rightarrow \begin{array}{l} \text{disequilibrium} \\ \text{conservation} \end{array}$$

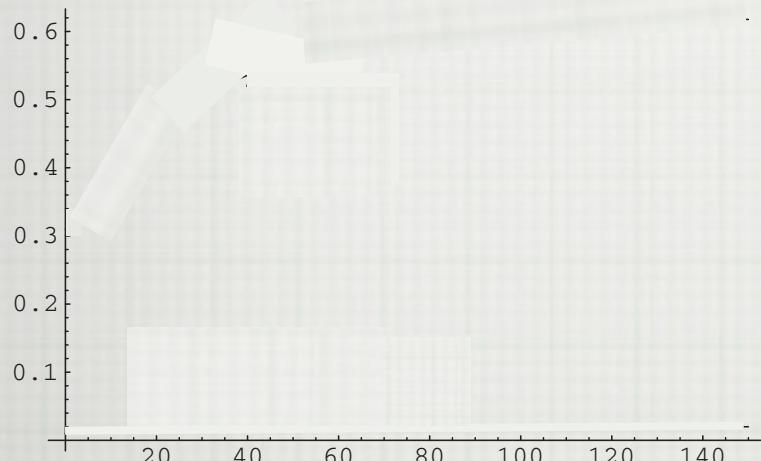
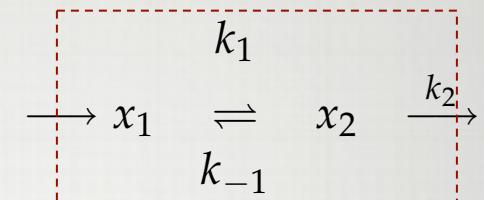
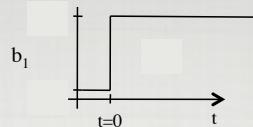


Dynamic Response of an Open System

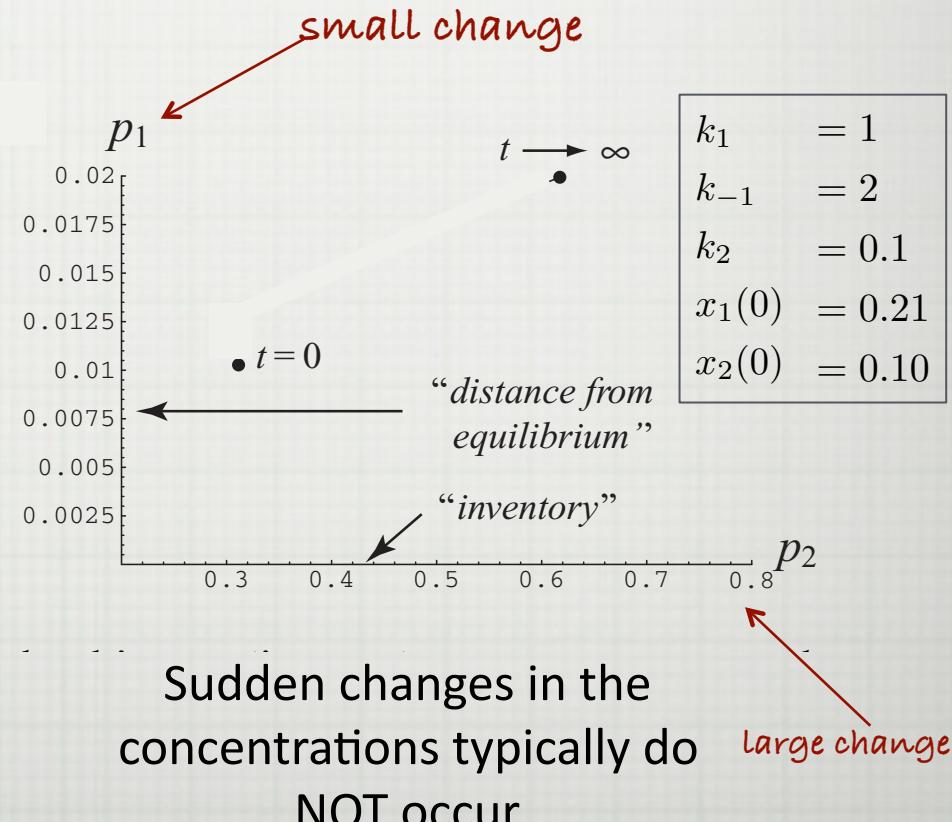


Dynamic Simulation from One Steady State to Another

(step change in b_1 from 0.01 to 0.02 at $t=0$)



Realistic perturbations are in the boundary fluxes



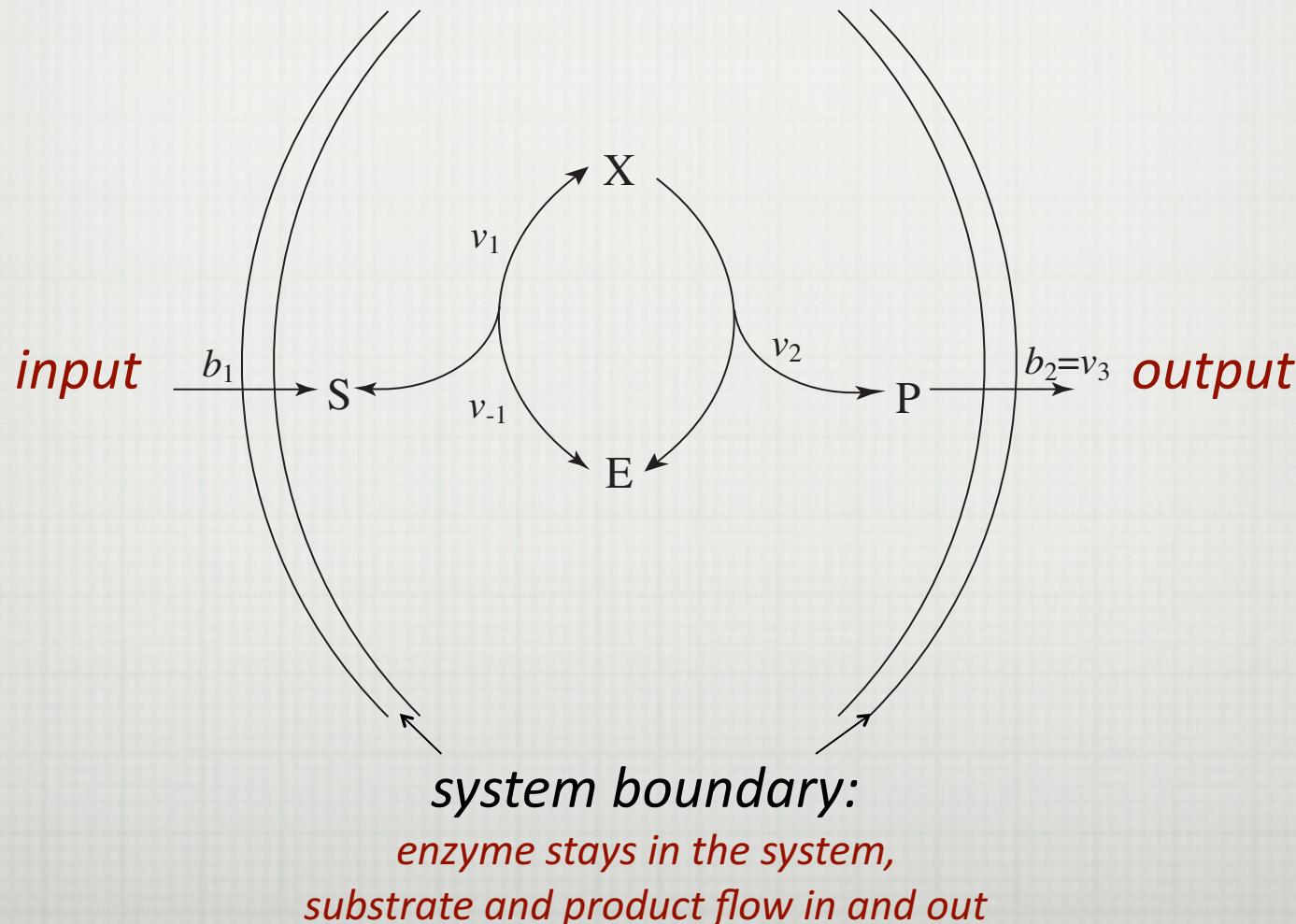
Some Lessons

- Open systems are in a steady state and respond to external stimuli
 - Can solve for stst concentrations by putting $\bullet \frac{dx}{dt} = 0$, and thus $\mathbf{Sv}(x_{ss}) = \mathbf{Sv}_{ss} = 0$
 - Can then solve for stst fluxes using
 - $\mathbf{v}_{ss} = \mathbf{v}(x_{ss}, \mathbf{k})$
- Changes from steady state
 - Changes in boundary fluxes are realistic
 - Changes in internal concentrations are not
- Relative rates of internal vs. exchange fluxes are important
 - If internal dynamics are ‘fast’ we may not need to characterize

Towards a more realistic situation

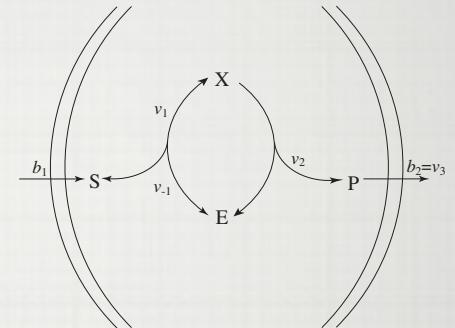
THE MICHAELIS-MENTEN MECHANISM IN AN OPEN SETTING

Michaelis-Menten Mechanism in an Open Setting



The Michaelis-Menten reaction

The basic equations



$$\begin{array}{rclcrcl} ds/dt & = & b_1 - k_1 es + k_{-1} x & & s(t=0) & = & s_0 \\ dx/dt & = & k_1 es - (k_{-1} + k_2)x & & x(t=0) & = & x_0 \\ de/dt & = & -k_1 es + (k_{-1} + k_2)x & & e(t=0) & = & e_0 \\ dp/dt & = & k_2 x - k_3 p & & p(t=0) & = & p_0 \end{array}$$

$$b_2 = v_3 = k_2 x$$

The stoichiometric matrix

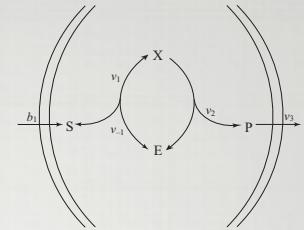
$$\mathbf{S} = \begin{pmatrix} b_1 & v_1 & v_{-1} & v_2 & b_2 = v_3 \\ 1 & -1 & 1 & 0 & 0 \\ 0 & -1 & 1 & 1 & 0 \\ 0 & 1 & -1 & -1 & 0 \\ 0 & 0 & 0 & 1 & -1 \end{pmatrix} \begin{matrix} s \\ x \\ e \\ p \end{matrix}$$

$m \times n = 4 \times 5$ and $r= 3$

$\text{Dim}(\text{Null}(S)) = 5-3=2$: two-dimensional *stst* flux space

$\text{Dim}(L.\text{Null}(S)) = 4-3=1$ – one conservation variable: $e+x$

The Steady State Solution



$$\mathbf{S}\mathbf{v}(\mathbf{x}_{ss}) = \mathbf{S}\mathbf{v}_{ss} = 0$$

$$\begin{aligned}\mathbf{v}_{ss} &= (b_1, k_1 e_{ss} s_{ss}, k_{-1} x_{ss}, k_2 x_{ss}, k_3 p_{ss}) \\ &= a(1, 1, 0, 1, 1) + b(0, 1, 1, 0, 0), \quad a \geq 0, b \geq 0\end{aligned}$$

$$x_{ss} = b_1/k_2, \quad p_{ss} = b_1/k_3, \quad \text{and} \quad e_{ss} = e_t - x_{ss} = e_t - b_1/k_2$$

the steady state concentrations

$$s_{ss} = \left(\frac{k_2}{k_1} \right) \left(\frac{k_{-1}/k_2 + 1}{e_t k_2 / b_1 - 1} \right)$$

the steady state flux balances

$$b_1 = v_1 - v_{-1} = v_2 = v_3$$

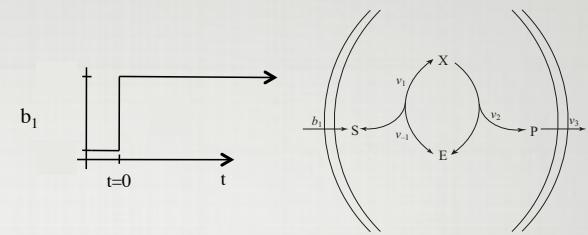
and the detailed flux solution is

$$\begin{aligned}\mathbf{v}_{ss} &= (b_1, b_1(1 + k_{-1}/k_2), b_1 k_{-1}/k_2, b_1, b_1) \\ &= a(1, 1, 0, 1, 1) + b(0, 1, 1, 0, 0), \quad a = b_1, b = b_1 k_{-1}/k_2\end{aligned}$$

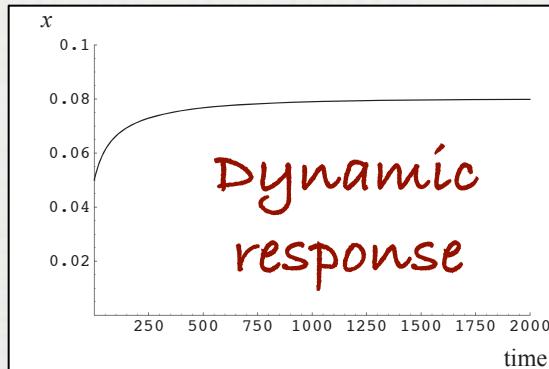
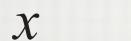
as before, the internal pathway has a flux of (k_{-1}/k_2) times that of the through pathway

Dynamic Response

Shift $b_1=0.025$ to 0.04 @ t=0

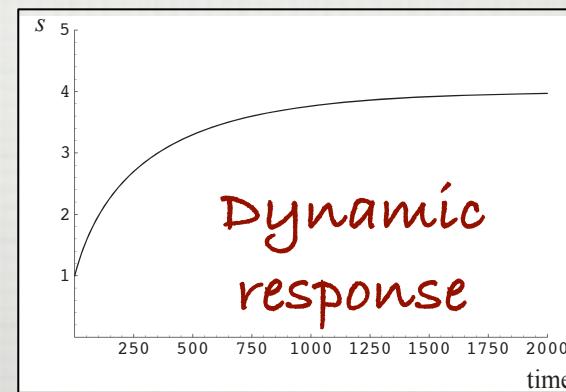
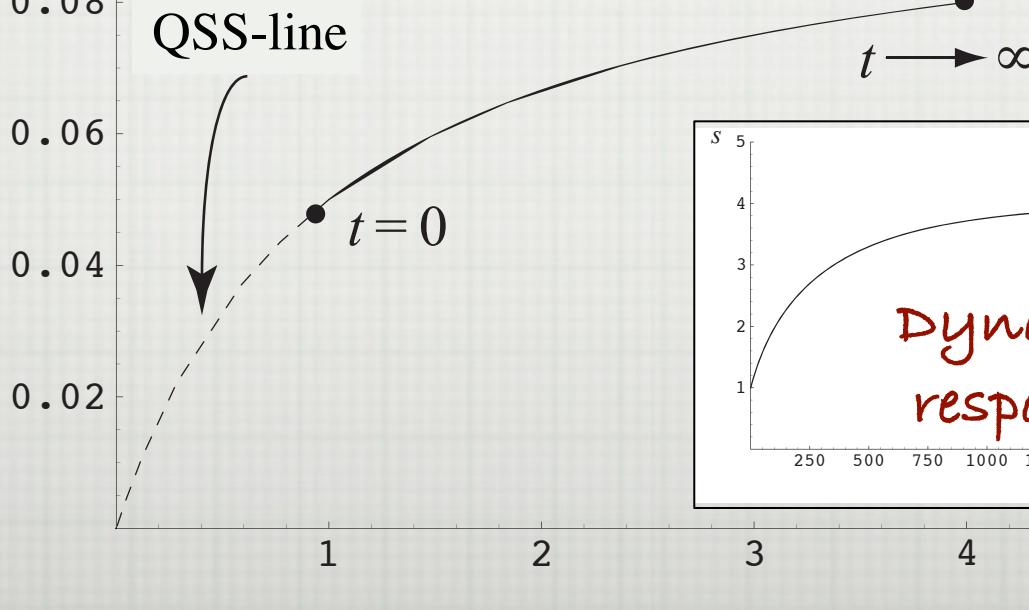


Phase portrait

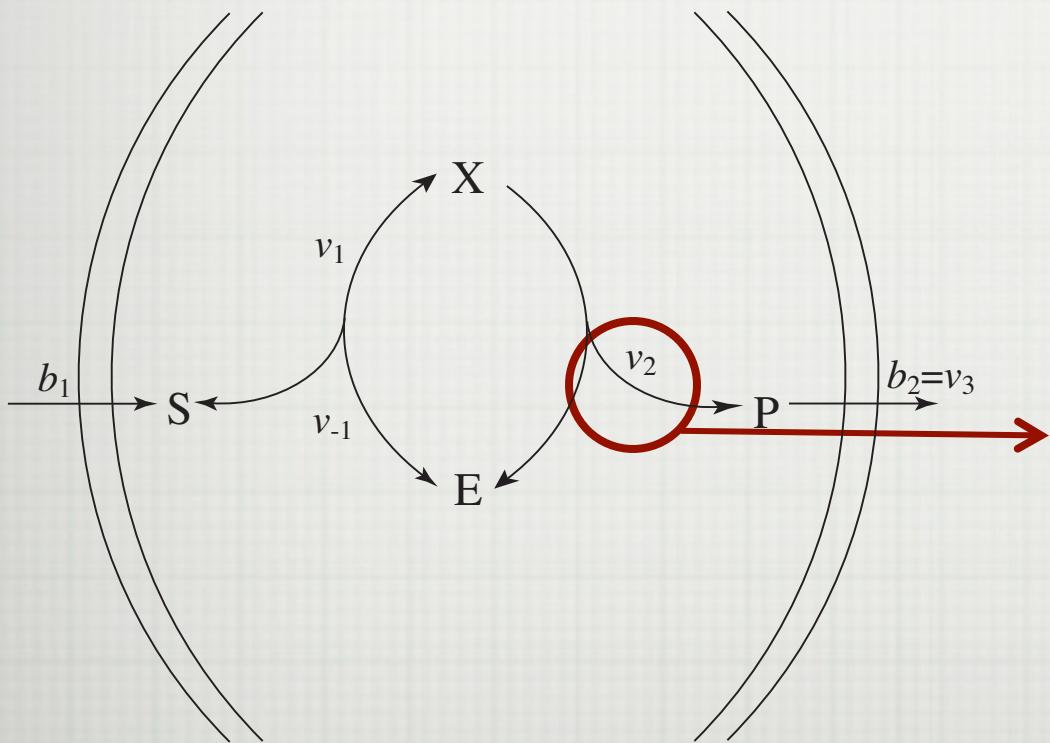


$$\begin{aligned} k_1 &= 1 \\ k_{-1} &= k_2 = 1/2 \\ k_3 &= 1/10 \\ e_t &= 1/10 \end{aligned}$$

QSS-line



Internal Capacity Constraint

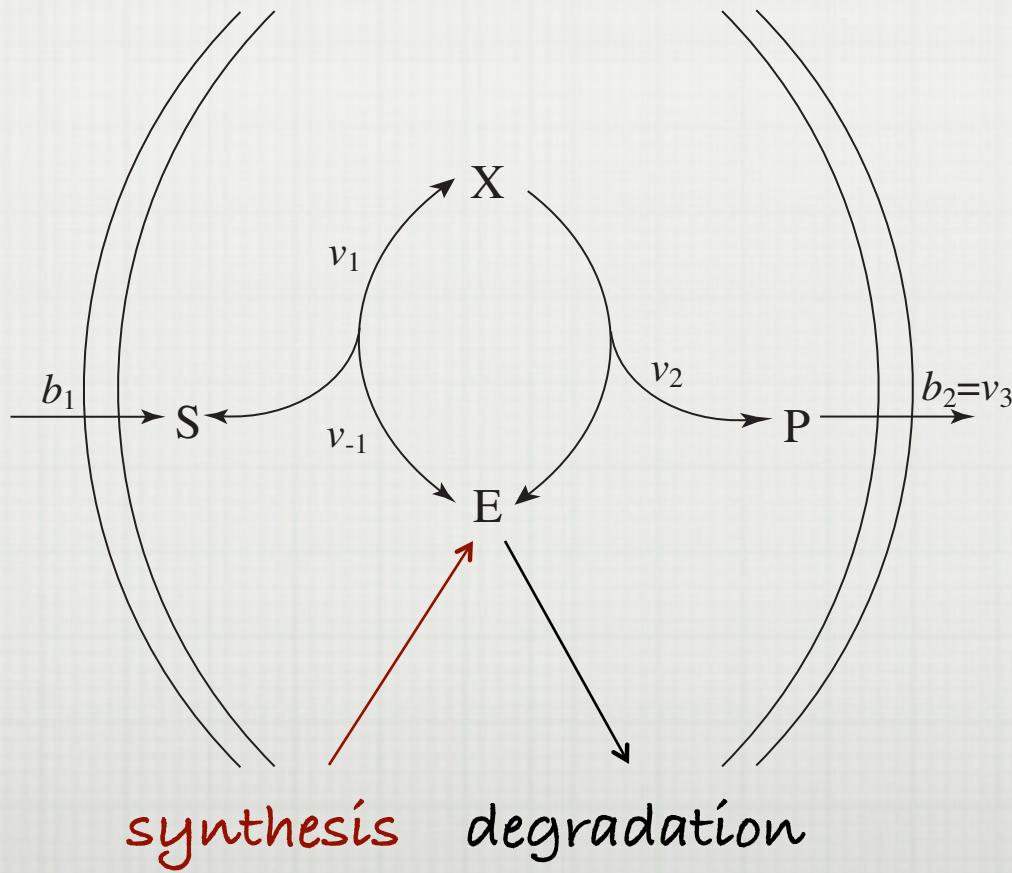


Steady state fluxes and maximum enzyme (e_{tot}) concentration give

$$b_1 = v_{2,ss} k_2 x_{2,ss} < k_2 e_{tot}$$

b_1 can be set to overcome the capacity of the system

Long-term adaptive response: increased enzyme synthesis



See Chapter 8 for an example

Summary

- Open systems reach a steady state (homeostasis)
- Closed systems reach equilibrium.
- Living systems are open systems that continually exchange mass and energy with the environment.
- Continual net throughput leads to a homeostatic state that is an energy dissipative state.
- Time scale separation between internal and exchange fluxes is important.
- Internal capacities can be exceeded:
 - Exchange fluxes are bounded: $0 < b_1 < b_{1,\max}$