Dynamical Systems for Biology - I

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Introduction

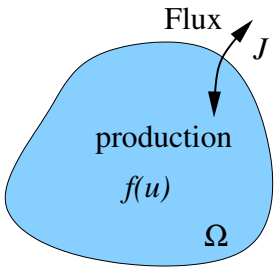
Biology is characterized by change. A major goal of modeling is to quantify how things change.

Fundamental Conservation Law:

$$\frac{d}{dt}(\text{stuff in } \Omega) = \text{rate of transport} + \text{rate of production}$$

In math-speak:

$$\frac{d}{dt}\int_\Omega u dV = \int_{\partial\Omega} J \cdot n ds + \int_\Omega f dv$$



where u is the density of the measured quantity, J is the flux of u across the boundary of Ω, f is the production rate density, and Ω is the domain under consideration (a cell, a room, a city, etc.)

Basic Chemical Reactions

$$A \xrightarrow{k} B$$

then

$$\frac{da}{dt} = -ka = -\frac{db}{dt}.$$

With back reactions,

$$A \underset{}{\overset{\rightarrow}{\leftarrow}} B$$

then

$$\frac{da}{dt} = -k_+ a + k_- b = -\frac{db}{dt}.$$

At steady state,

$$a = a_0 \frac{k_-}{k_- + k_+}.$$

Bimolecular Chemical Reactions

$$A + C \xrightarrow{k} B$$

then

$$\frac{da}{dt} = -kca = -\frac{db}{dt} \quad \text{(the "law" of mass action).}$$

With back reactions,

$$A + C \overrightarrow{\leftarrow} B$$

$$\frac{da}{dt} = -k_+ca + k_-b = -\frac{db}{dt}.$$

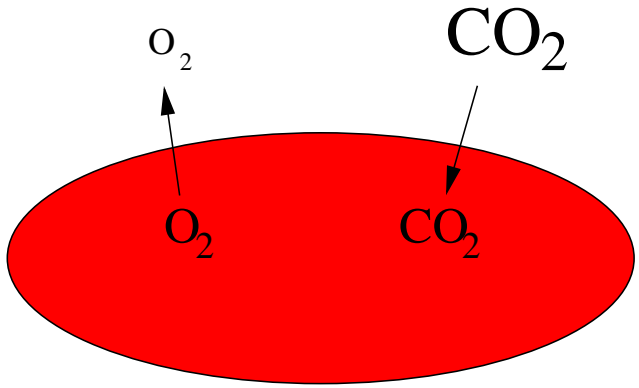
In steady state, $-k_+ca + k_-b = 0$ and $a + b = a_0$, so that

$$a = \frac{k_-a_0}{k_+c+k_-} = \frac{K_{eq}a_0}{K_{eq}+c}.$$

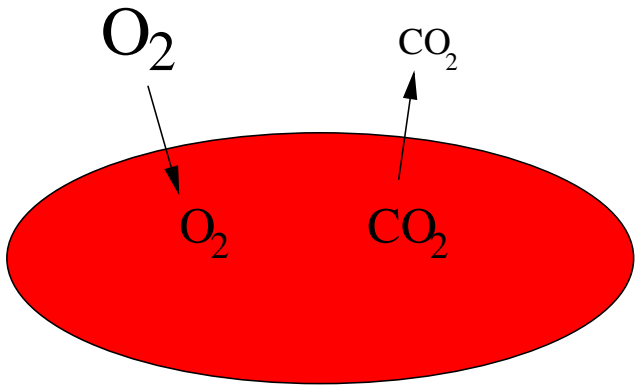
Remark: c can be viewed as controlling the amount of a.

Example:Oxygen and Carbon Dioxide Transport

Problem: If oxygen and carbon dioxide move into and out of the blood by diffusion, their concentrations cannot be very high (and no large organisms could exist.)



In Tissue



In Lungs

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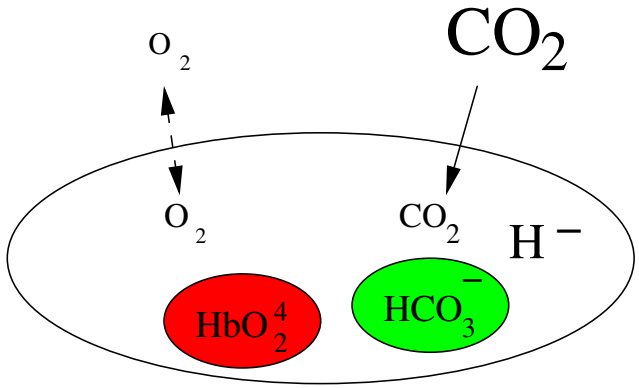

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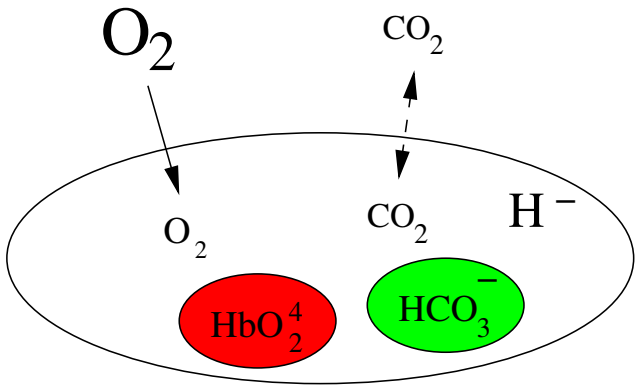

In Lungs

Problem solved: Chemical reactions that help enormously:

$$CO_2(+H_2O) \rightleftarrows HCO_3^+ + H^- \qquad Hb + 4O_2 \rightleftarrows Hb(O_2)^4$$

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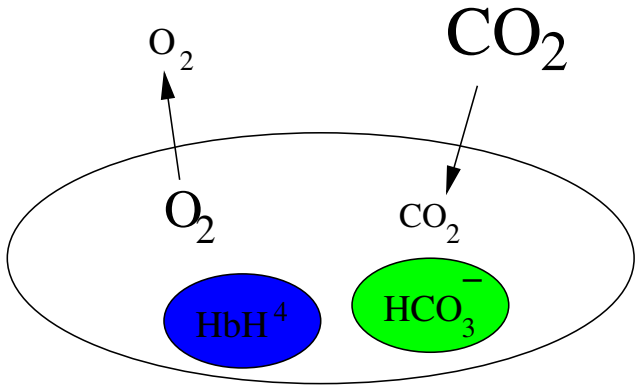

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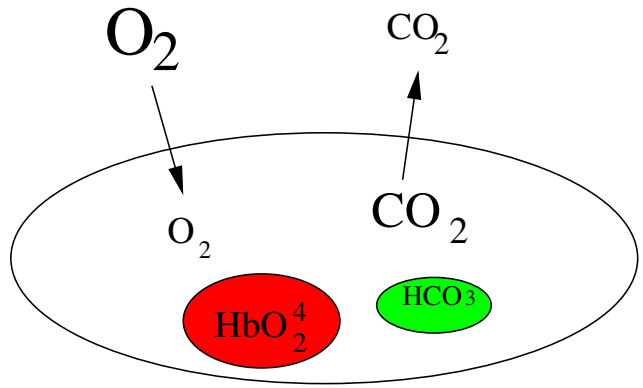

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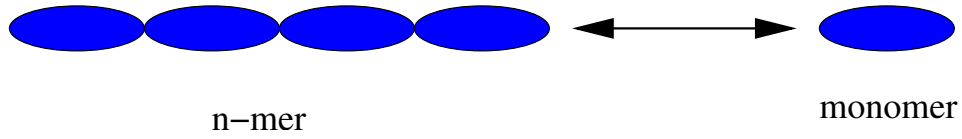
$$CO_2(+H_2O) \rightleftarrows HCO_3^+ + H^- \qquad Hb + 4O_2 \rightleftarrows Hb(O_2)^4$$

Hydrogen competes with oxygen for hemoglobin binding.

Example II: Polymerization



$$A_n + A_1 \rightleftarrows A_{n+1}$$

$$\frac{da_n}{dt} = k_- a_{n+1} - k_+ a_n a_1$$

Question: If the total amount of monomer is fixed, what is the steady state distribution of polymer lengths?

Enzyme Kinetics

$$S + E \overset{\rightarrow}{\leftarrow} C \overset{k_2}{\rightarrow} P + E$$

$$\frac{ds}{dt} = k_- c - k_+ se$$
$$\frac{de}{dt} = k_- c - k_+ se + k_2 c = -\frac{dc}{dt}$$
$$\frac{dp}{dt} = k_2 c$$

Use that $e + c = e_0$, so that

$$\frac{ds}{dt} = k_-(e_0 - e) - k_+ se$$
$$\frac{de}{dt} = -k_+ se + (k_- + k_2)(e_0 - e)$$

The QSS Approximation

Assume that the equation for e is "fast", and so in quasi-equilibrium. Then,

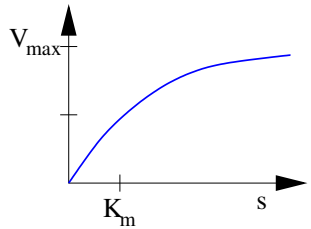
$$(k_- + k_2)(e_0 - e) - k_+ s e = 0$$

or

$$e = \frac{(k_- + k_2)e_0}{k_- + k_2 + k_+ s} = e_0 \frac{K_m}{s + K_m} \text{ (the qss approximation)}$$

Furthermore, the "slow reaction" is

$$\frac{dp}{dt} = -\frac{ds}{dt} = k_2 c = k_2 e_0 \frac{s}{K_m + s}$$



This is called the Michaelis-Menten reaction rate, and is used routinely (without checking the underlying hypotheses).

Enzyme Interactions

1) Enzyme activity can be inhibited (or poisoned). For example,

$$S + E \rightleftarrows C \overset{k_2}{\rightarrow} P + E \qquad I + E \rightleftarrows C_2$$

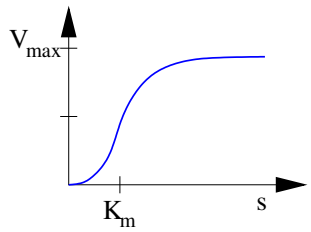
Then,

$$\frac{dp}{dt} = -\frac{ds}{dt} = k_2 e_0 \frac{s}{s + K_m(1 + \frac{i}{K_i})}$$

2) Enzymes can have more than one binding site, and these can "cooperate".

$$S + E \rightleftarrows C_1 \overset{k_2}{\rightarrow} P + E \qquad S + C_1 \rightleftarrows C_2 \overset{k_4}{\rightarrow} P + E$$

$$\frac{dp}{dt} = -\frac{ds}{dt} = V_{max} \frac{s^2}{K_m^2 + s^2}$$



Example:SIR

Consider an infectious disease with dynamics

$$S \overset{k_s I}{\rightarrow} I \overset{k_i}{\rightarrow} R$$

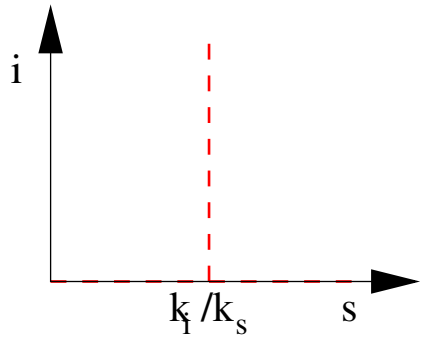
(R = permanent immunity - or death)

Equations are

$$\frac{ds}{dt} = -k_s s i$$
$$\frac{di}{dt} = k_s s i - k_i i$$

Nullclines for I ($\frac{dI}{dt} = 0$)

$i = 0$ and $s = \frac{k_i}{k_s}$



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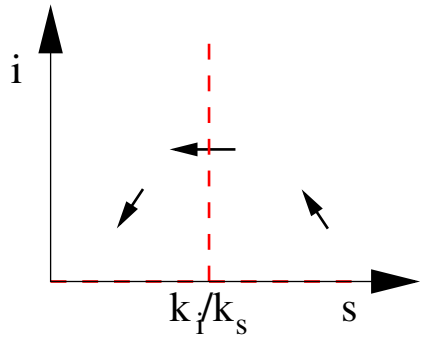

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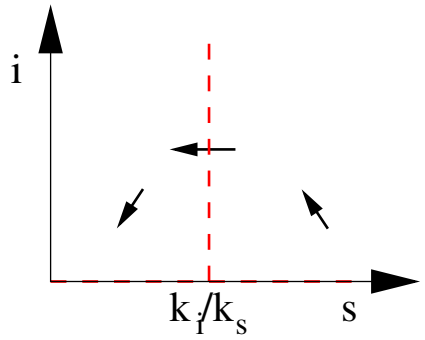

Conclusion: Epidemic can occur only if $S_0 > \frac{k_i}{k_s}$.

Example:SIRS

Suppose immunity is not permanent:

$$S \xrightarrow{I} I \xrightarrow{k_i} R \xrightarrow{k_r} S$$

Equations are

$$\frac{ds}{dt} = -k_s si + k_r r$$

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$r + s + i = n$ is fixed

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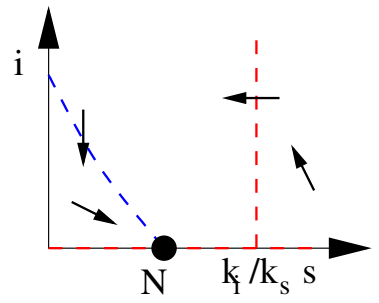
$$s = \frac{k_r(N-i)}{k_s i + k_r}$$



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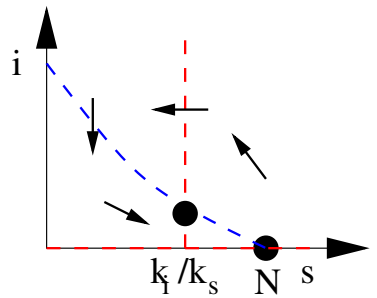

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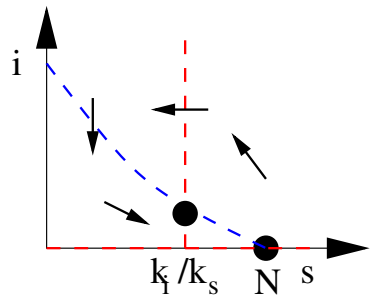


Conclusion: For $N > \frac{k_i}{k_s}$, disease is endemic.

Example: Quorum Sensing

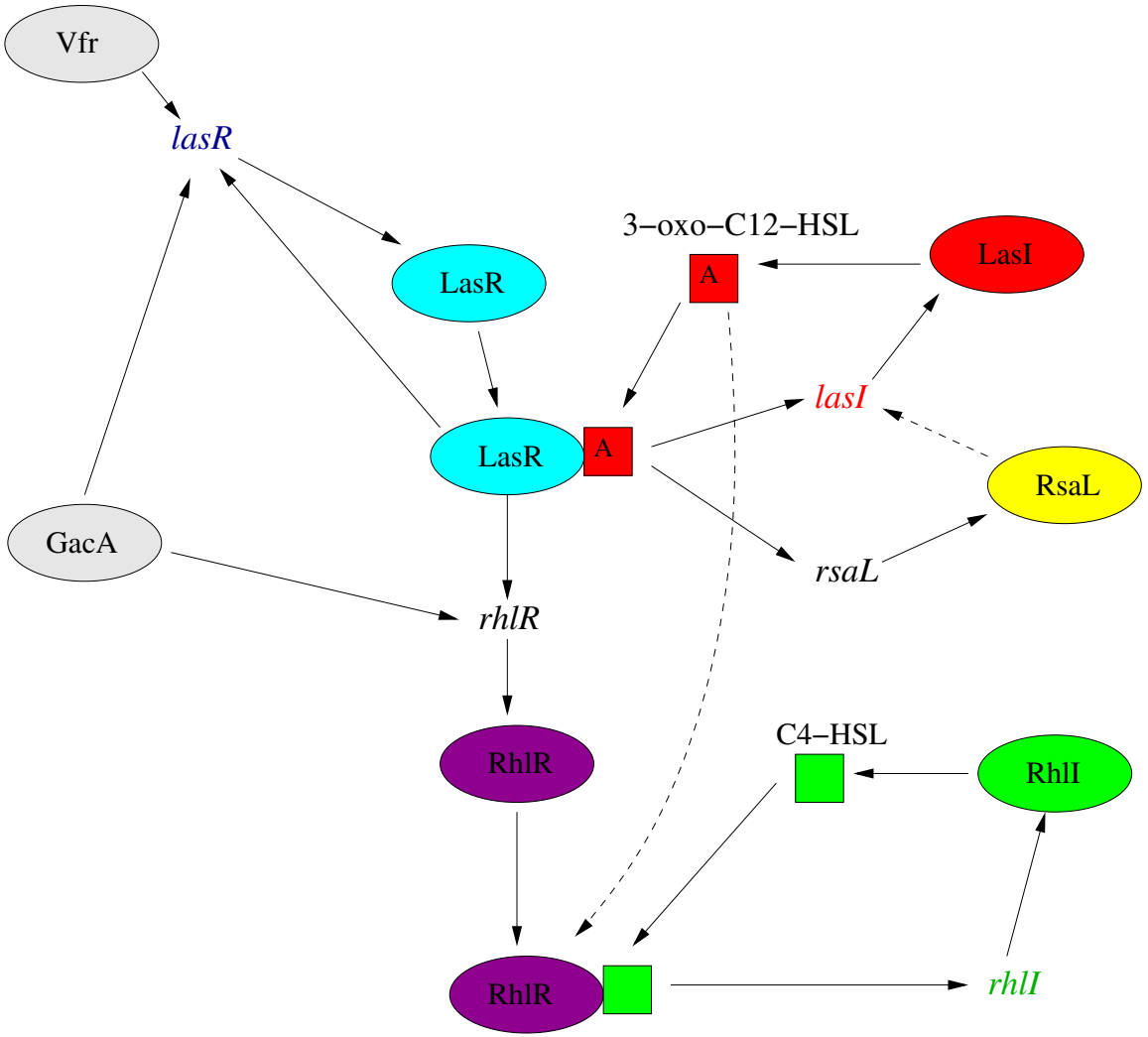
Quorum sensing: The ability of a bacterial colony to sense its size and regulate its activity in response.

Examples: *Vibrio fisheri*, *P. aeruginosa*

P. Aeruginosa:

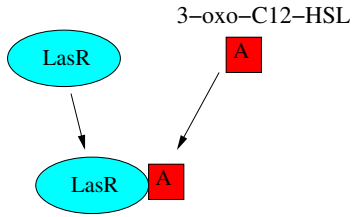
- Major cause of hospital infection in the US.
- Major cause of death in intubated Cystic Fibrosis patients.
- In planktonic form, they are non-toxic, but in biofilm they are highly toxic and well-protected by the polymer gel in which they reside. However, they do not become toxic until the colony is of sufficient size, i.e., quorum sensing.

Biochemistry of Quorum Sensing



Modeling Biochemical Reactions

Bimolecular reaction $A + R \longleftrightarrow P$



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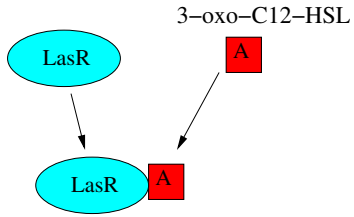

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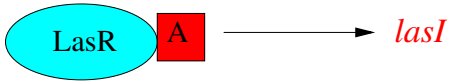
Production of mRNA $\xrightarrow{P} l$



$$\frac{dl}{dt} = \frac{V_{max} P}{K_l + P} - k_{-l} l$$

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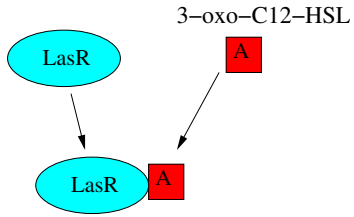

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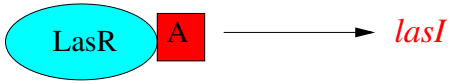

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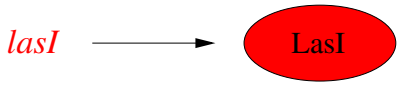
Enzyme production $l \rightarrow L$



$$\frac{dL}{dt} = k_l l - K_L L$$

Full system of ODE's

$$\frac{dP}{dt} = k_{RA}RA - k_P P$$

$$\frac{dR}{dt} = -k_{RA}RA + k_P P - k_R R + k_1 r,$$

$$\frac{dA}{dt} = -k_{RA}RA + k_P P + k_2 L - k_A A,$$

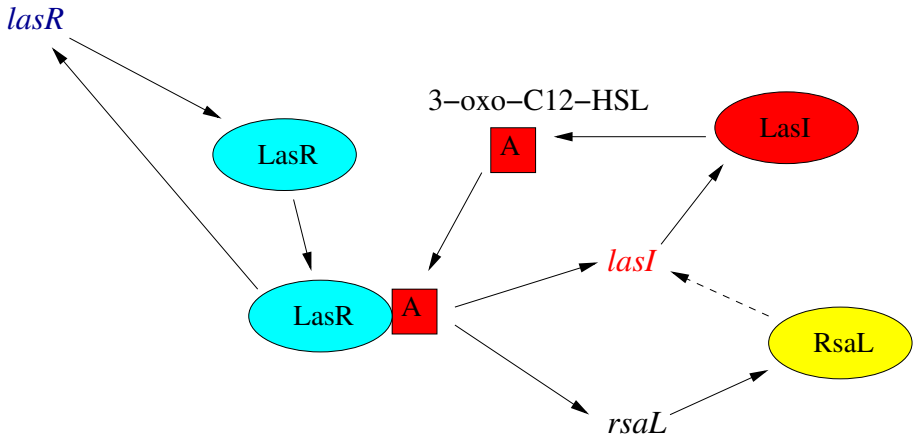
$$\frac{dL}{dt} = k_3 l - k_l L,$$

$$\frac{dS}{dt} = k_4 s - k_S S,$$

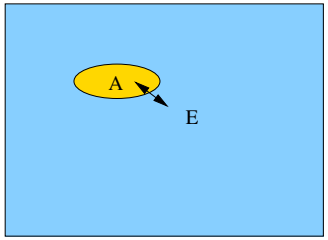
$$\frac{ds}{dt} = V_s \frac{P}{K_S+P} - k_s s,$$

$$\frac{dr}{dt} = V_r \frac{P}{K_r+P} - k_r r + r_0,$$

$$\frac{dl}{dt} = V_l \frac{P}{K_l+P} \frac{1}{K_S+S} - k_l l + l_0$$



Diffusion



$$\frac{dA}{dt} = F(A,R,P) + \delta(E-A)$$

$$\frac{dE}{dt} = -k_E E + \delta(A-E)$$

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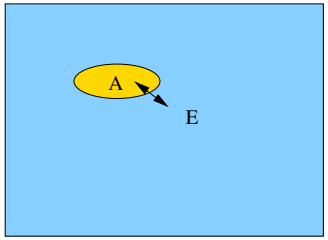

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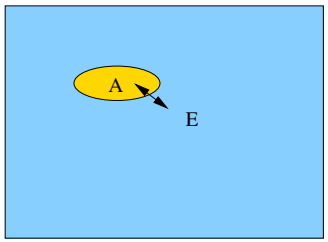
rate of change,

Diffusion



$$\frac{dA}{dt} = \boxed{F(A,R,P)} + \delta(E-A)$$

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rate of change, production or degradation rate,

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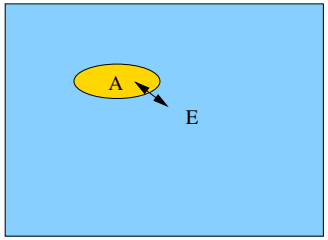

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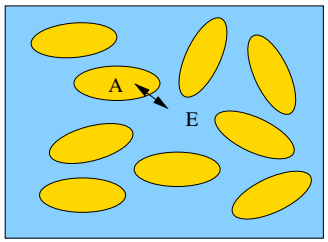
rate of change, production or degradation rate, diffusive exchange,

Diffusion



$$\frac{dA}{dt} = F(A,R,P) + \delta(E-A)$$

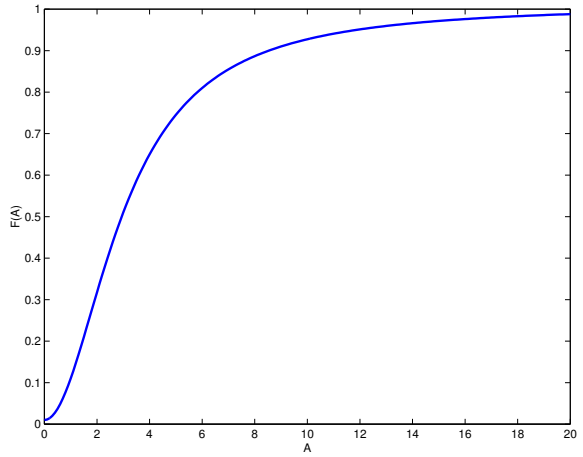
$$\boxed{(1-\rho)}\left(\frac{dE}{dt} + K_E E\right) = \boxed{\rho}\,\delta(A-E)$$

rate of change, production or degradation rate, diffusive exchange, density dependence.

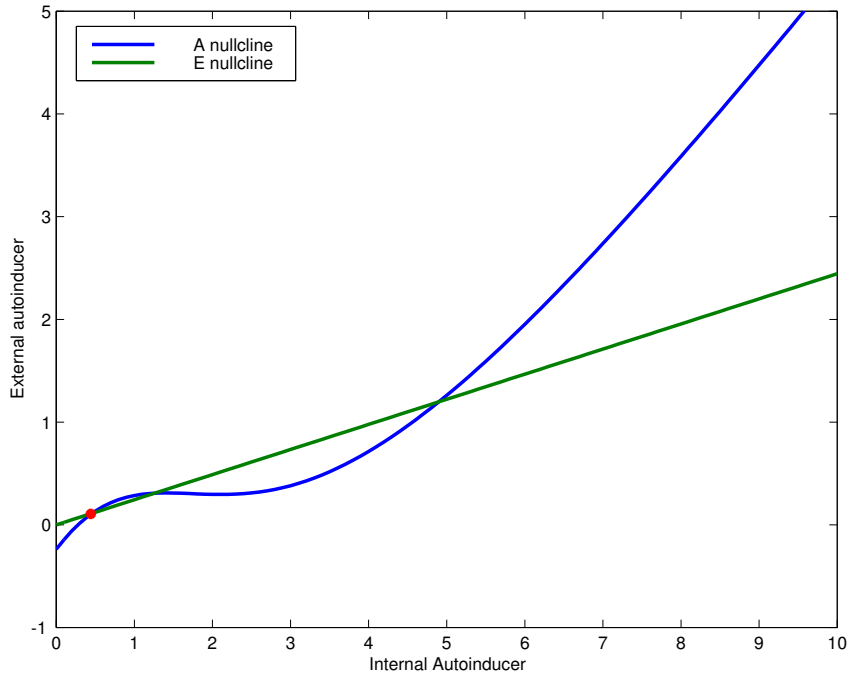
Model Reduction and Analysis

Apply QSS reduction:

$$\frac{dA}{dt} = F(A) + \delta(E - A), \qquad (1-\rho)(\frac{dE}{dt} + k_E E) = \rho\delta(A - E)$$



Two Variable Phase Portrait



$$\frac{dA}{dt} = F(A) + \delta(E - A), \qquad E = A - \frac{1}{\delta}F(A)$$

$$\frac{dE}{dt} = -k_E E + \frac{\rho}{1-\rho}\delta(A - E) \qquad A = (\frac{1-\rho}{\rho\delta}k_E + 1)E$$

Summary

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- Because reactions can occur on many different time scales, quasi-steady state approximations are often quite useful;
- For two variable systems, much can be learned from the "phase portrait".