Law of Mass Action - simple
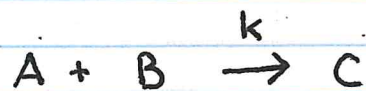
Rate of change of concentration is proportional to the product of reactants

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

results in system

$$A' = -kAB$$

$$B' = -KAB$$

$$C' = +KAB$$

where k is the reaction rate.

Remarks

(1)   Concentration usually in molarity M

$$[A] = 1M \iff \text{liter contains } N_a = 6.02 \times 10^{23} \text{ molecules}$$

Mass action law only works for molarity. Once differential eqns have been found they can be converted to gm/liter use the gram molecular weights.

(2)   AB   proportional to total number of reactions (collisions) at any given instant

Arrhenius Theory

$$k = \alpha e^{-E_a/RT}$$

Reaction rate is proportional to the exponential term where

E_a = activation energy for reaction $\qquad [E_a] = J/mole$

T = temperature $\qquad [T] = Kelvin$
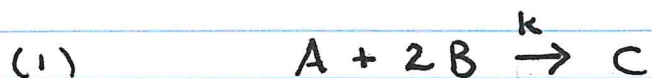
R = Gas constant = 8.314 J/mole/K
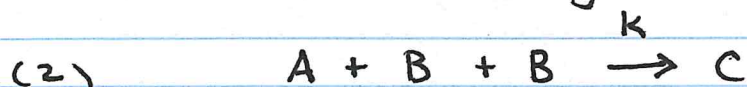
In some cases $\alpha = \alpha_0 T^n$ for $n \in (-1, 1)$.

Note that $T \uparrow$ implies rate $k \uparrow$

EXAMPE Stoichiometric coefficients

(1) $\qquad A + 2B \xrightarrow{k} C$

Number of possible collisions is $[A][B]^2$ so (1) should be thought of as

(2) $\qquad A + B + B \xrightarrow{k} C$

having "three" reactants. L.O.M.A. then $\Rightarrow$

$$\frac{dC}{dt} = + kAB^2$$

Here "2" in eqn (1) is a stoichiometric coeff.

Law of Mass Action — general
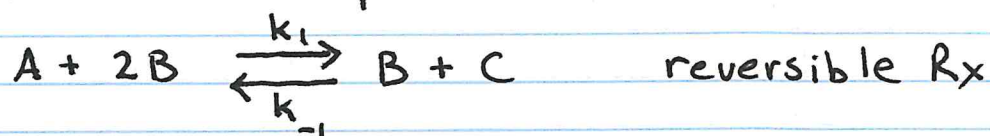
(1) $\quad A + mB \xrightarrow{k} nB + pC$

(2) $\quad kAB^m = -\dfrac{dA}{dt} = \dfrac{1}{p}\dfrac{dC}{dt} = \dfrac{1}{(n-m)}\dfrac{dB}{dt}$

The stoichiometric coefficients reflect
the fact for every molecule of A

$\quad p$ molecules of C produced

$\quad (m-n)$ net loss of molecules of B

EXAMPLE   Reaction equations for

$$A + 2B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B + C \qquad \text{reversible Rx}$$

$$A + C \xrightarrow{k_2} B \qquad \text{irreversible Rx}$$

Is a set of <u>three</u> chem. Rx eqns

$$A' = -k_1 AB^2 + k_{-1} BC - k_2 AC$$

$$B' = -k_1 AB^2 - k_{-1} BC + k_2 AC$$

$$C' = k_1 AB^2 - k_{-1} BC - k_2 AC$$

<u>EXAMPLE</u>   Auto catalytic / Stoichiometry

$$A + 3B \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} B + C + D$$

$$A + D \xrightarrow{k_2} B$$

$$B + 2C \xrightarrow{k_3} A$$
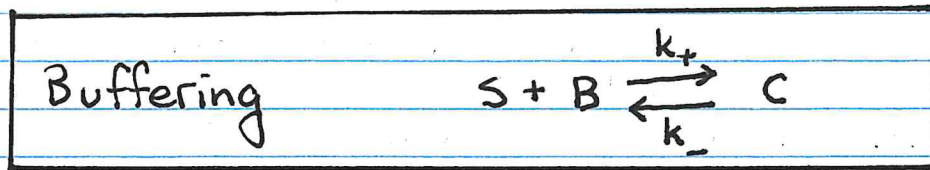
Reaction equations for A, B, C, D

$$A' = -k_1 AB^3 + k_{-1} BCD - k_2 AD + k_3 BC^2$$

$$B' = -2k_1 AB^3 + 2k_{-1} BCD + k_2 AD - k_3 BC^2$$

$$C' = k_1 AB^3 - k_{-1} BCD - 2k_3 BC^2$$

$$D' = k_1 AB^3 - k_{-1} BCD - k_2 AD$$

Reaction equations <u>autocatalytic</u> since
A is ultimately involved in is' own creation.

$$\boxed{\text{Buffering} \qquad S + B \underset{k_-}{\overset{k_+}{\rightleftarrows}} C}$$

S = Substrate   (Ca^{2+})
B = Buffer   (Protein)
C = complex   (Protein $-Ca^{2+}$ complex)

Law of Mass Action

(1) $S' = -k_+ SB + k_- C$ $S(0) = S_0$
(2) $B' = -k_+ SB + k_- C$ $B(0) = B_0$
(3) $C' = k_+ SB - k_- C$ $C(0) = C_0$

Conservation of receptors

$$(B + C)' = 0$$

(4) $B + C = N = B_0 + C_0$ # receptor sites

Use (4) to simplify (1) – (3)

$$S' = f(B, S)$$
$$B' = f(B, S)$$

where

$$\boxed{f(B, S) = -k_+ SB + k_- (N - B)}$$

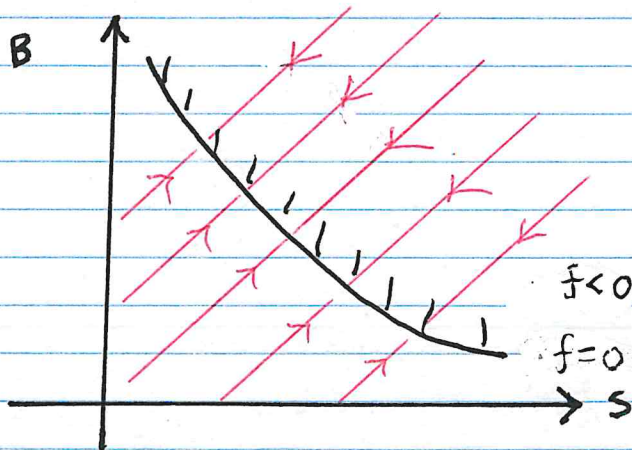The sign of f determines trajectory direction.

Sign of $f(S, B)$

$$f(S, B) \quad < 0$$

$$-k_+ SB + k_-(N-B) \quad < 0$$

$$-(k_+ S + k_-)B + k_- N \quad < 0$$

solving for B

$$\boxed{f < 0 \quad \Leftrightarrow \quad B < g(S) = \frac{K_E N}{K_E + S}}$$

where the equilibrium constant $K_E = \dfrac{k_-}{k_+}$

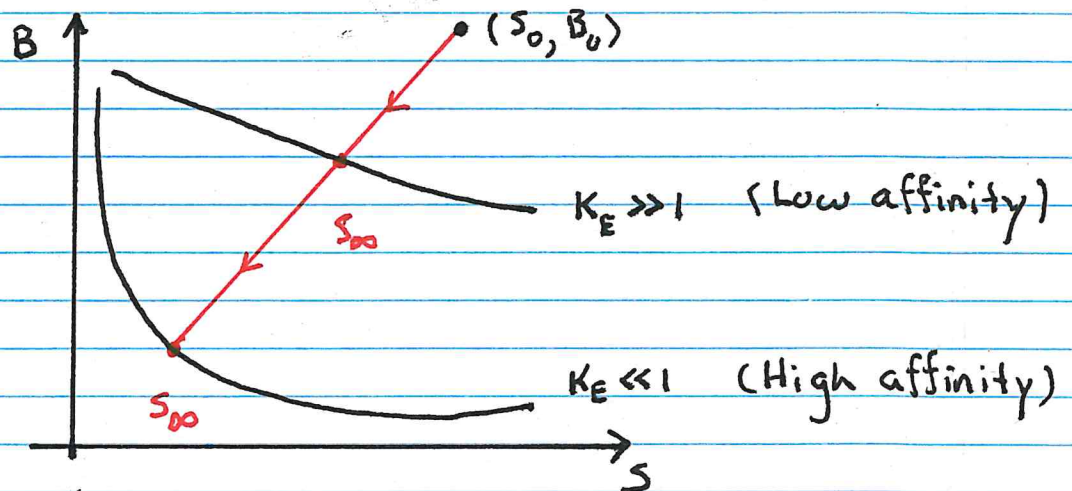physical region (shaded) for $c(0) = 0$

$f < 0$
$f = 0$

Notes

- $f = 0$ is a line of fixed points
- $f < 0$ is physical region since $\frac{dS}{dt} < 0$ there.
- $f = 0$ is a "stable invariant manifold"

Low and High affinity binding

Trajectories in the SB-plane have slope one
and approach the curve

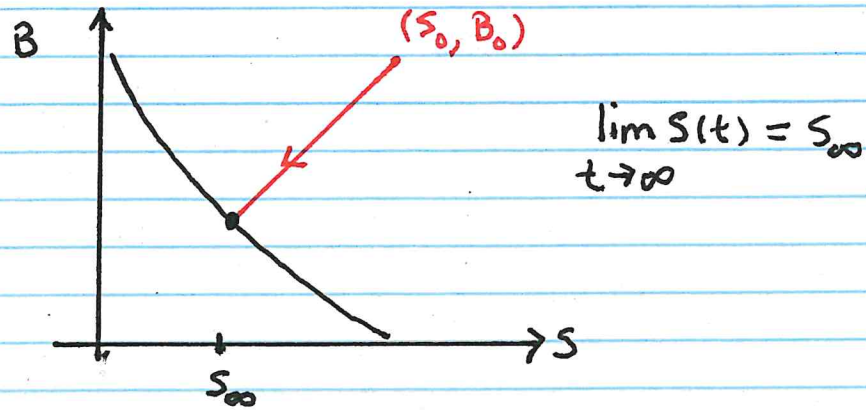$$B = g(S) = \frac{K_E N}{K_E + S} \qquad K_E = \frac{k_-}{k_+}$$

Consider the two cases $K_E \gg 1$ and $K_E \ll 1$

In the high affinity case the asymptotic value
S_∞ of S is smaller meaning more substrate
molecules are bound.

| $K_E \gg 1$ | Low Affinity | larger S_∞ |
| $K_E \ll 1$ | High Affinity | smaller S_∞ |

Asymptotic behavior

$$\lim_{t \to \infty} S(t) = S_\infty$$

S_∞ can be found as the intersection of the two curves

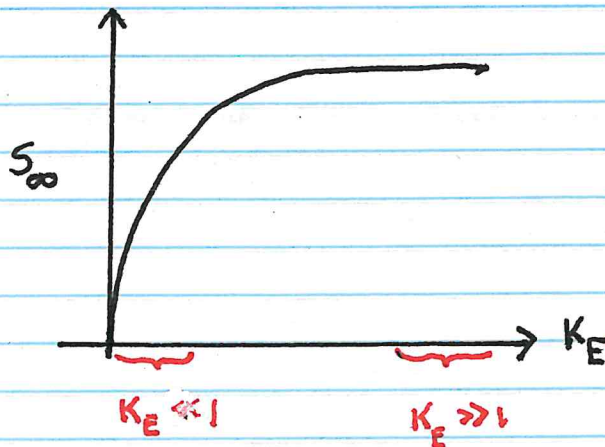$$B = S + \Delta \qquad\qquad \Delta = B_0 + S_0$$
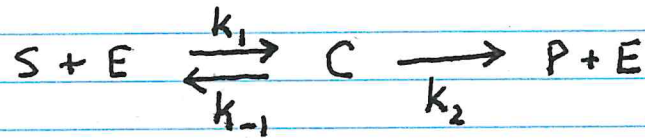
$$B = g(S)$$

Results in a quadratic eqn for S

(1)
$$\boxed{S + \Delta = \dfrac{K_E N}{K_E + S}}$$

Solving and plotting S_∞ versus K_E one gets

Michaelis-Menten Kinetics

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} P + E$$
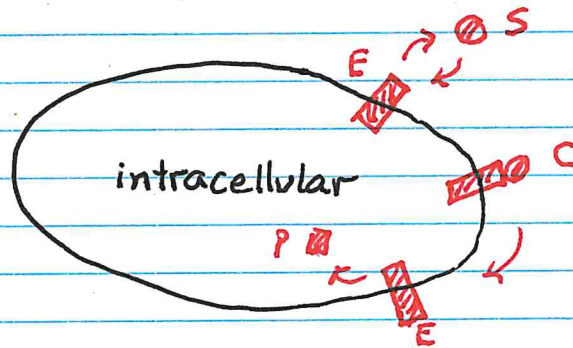
where

S = substrate   (small)
E = enzyme   (large)
C = complex
P = product

Can model cell nutrient uptake via membrane proteins E. Typically

$$E_0 \ll S_0$$

Law of Mass Action

$$(1) \quad \dot{S} = k_{-1} C - k_1 SE \qquad\qquad S(0) = S_0$$

$$(2) \quad \dot{E} = (k_{-1} + k_2) C - k_1 SE \qquad E(0) = E_0$$

$$(3) \quad \dot{C} = -\dot{E} \qquad\qquad\qquad C(0) = 0$$

$$(4) \quad \dot{P} = k_2 C \qquad\qquad\qquad P(0) = 0$$

Conservation of receptors: $E + C = E_0$

Nondimensionalization

$$s = S/_{S^*} \qquad e = E/_{E^*} \qquad c = C/_{C^*} \qquad p = P/_{P^*} \qquad \tau = t/_{t^*}$$

For the following choices

$$S^* = S_0 \qquad E^* = C^* = E_0 \qquad P^* = \frac{k_2}{k_1} \qquad t^* = \frac{1}{k_1 E_0}$$

one can derive the dimensionless equs for the dimensionless variables (s, e, c, p, τ)

$$
\begin{array}{lll}
(1) & s' = K_1 c - se & s(0) = 1 \\[2mm]
(2) & \varepsilon e' = K_2 c - se & e(0) = 1 \\[2mm]
(3) & \varepsilon c' = -K_2 c + se & c(0) = 0 \\[2mm]
(4) & p' = c & p(0) = 0
\end{array}
$$

where

$$\varepsilon = \frac{E_0}{S_0} \ll 1$$

and

$$K_1 = \frac{k_{-1}}{k_1 S_0} \qquad\qquad K_2 = \frac{k_{-1} + k_2}{k_1 S_0}$$

Notice that for positive k_1, k_{-1} and k_2

$$K_2 > K_1 \qquad\qquad \text{physicality condition}$$

Quasi Steady State (QSS)

Is a science term where one lets $\varepsilon \to 0$ as an approximation to (1)-(4). This yields from the $\varepsilon e'$ eqn

(5)
$$K_2 c - se = 0$$

Conservation of receptors (dimensionless) is:

(6)
$$e + c = 1$$

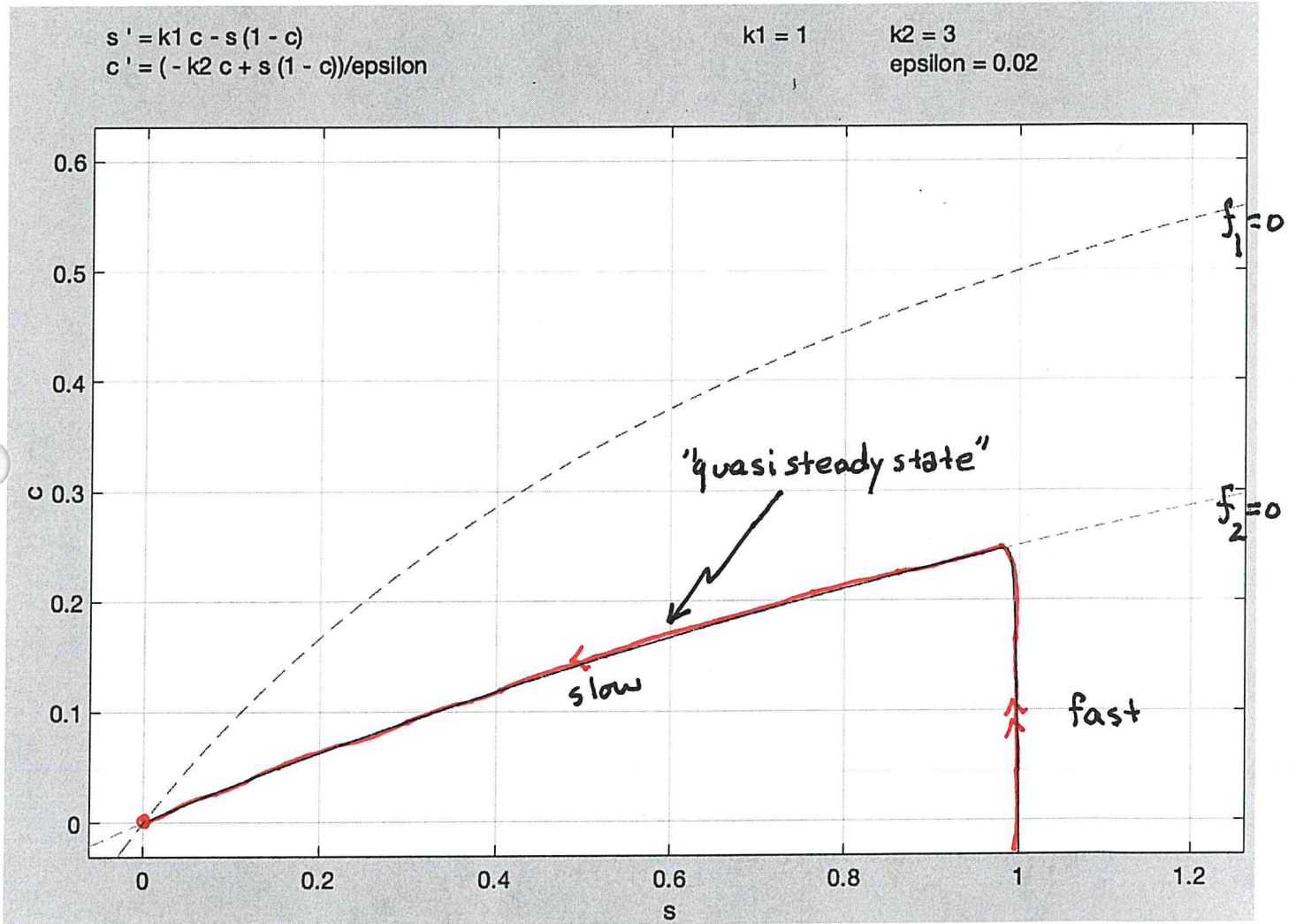One may solve the system (5)-(6) for e in terms of s or (c in terms of s)

$$e = \frac{K_2}{K_2 + s} \qquad c = \frac{s}{K_2 + s}$$

Next page shows a typical numerical solution of (1)-(4)

$$K_1 = 1 \qquad K_2 = 3$$

Typical Numerical solution

$$K_2 > K_1 \qquad \varepsilon \ll 1$$

s' = k1 c - s (1 - c)   k1 = 1   k2 = 3
c' = (- k2 c + s (1 - c))/epsilon   epsilon = 0.02

"quasi steady state"

$f_1 = 0$

$f_2 = 0$

slow

fast

s and c nullclines shown

FAST-SLOW TIME APPROXIMATIONS

Using conservation of receptors

$$e + c = 1$$

in (1)-(3) we get a planar system

(5)
$$\frac{ds}{d\tau} = f_1(s,c) = K_1 c - s(1-c)$$

$$\varepsilon \frac{dc}{d\tau} = f_2(s,c) = -K_2 c + s(1-c)$$

along with initial conditions:

$$s(0) = 1 \qquad c(0) = 0$$

These equations are <u>exact</u>.

Nullclines/Equilibrium

Are easy to define

$$f_1 = 0 \qquad \Leftrightarrow \qquad c = H_1(s) = \frac{s}{K_1 + s}$$

$$f_2 = 0 \qquad \Leftrightarrow \qquad c = H_2(s) = \frac{s}{K_2 + s}$$

From these it is easy to show $(0,0)$ is the sole equilibrium.

To understand the solutions of system (5)
we introduce fast and slow times

$$\tau \qquad\qquad \text{slow time}$$

$$t = \frac{\tau}{\varepsilon} \qquad\qquad \text{fast time}$$

Since $\varepsilon \ll 1$, only a small change in
the slow time τ is needed to make
the fast time change by order 1 or $O(1)$
For instance, $\varepsilon = 10^{-3}$ and $\tau = 2 \times 10^{-3}$
yields $t = 2$.

Lastly, system (5) can be expressed
with either time using the chain rule.

$$\frac{ds}{d\tau} = \frac{ds}{dt}\frac{dt}{d\tau} = \frac{1}{\varepsilon}\frac{ds}{dt}$$

$\dfrac{ds}{d\tau} = f_1(s,c)$	$\dfrac{ds}{dt} = \varepsilon f_1(s,c)$
$\varepsilon\dfrac{dc}{d\tau} = f_2(s,c)$	$\dfrac{dc}{dt} = f_2(s,c)$
SLOW SUBSYSTEM	FAST SUBSYSTEM
τ = slow time	t = fast time

(SS) (FS)

Leading order Fast Subsystem (FS)

Le.

smaller higher order terms

$$S(t) = S_0(t) + \varepsilon S_1(t) + \cdots$$

$$C(t) = C_0(t) + \varepsilon C_1(t) + \cdots$$

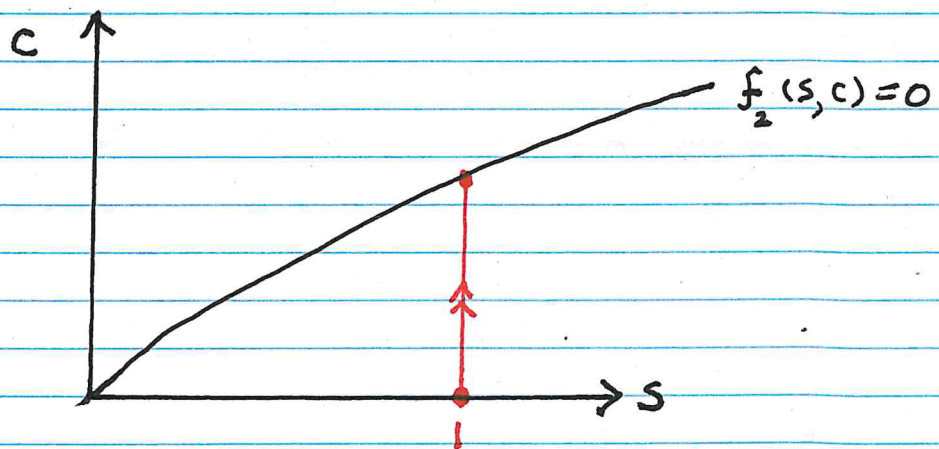in the (FS) yields leading order behavior

$$\left\| \begin{array}{ll} \dfrac{dS_0}{dt} = 0 & S_0(0) = 1 \\[2mm] \dfrac{dC_0}{dt} = f_2(S_0, C_0) & C_0(0) = 0 \end{array} \right\|$$

Solving with initial conditions

$$S_0(t) = 1$$

$$C_0(t) = \frac{1}{\mu} (1 - \exp(-\mu t)) \qquad \mu \equiv K_2 + 1$$

Note $C_0(t) \to \dfrac{1}{K_2 + 1}$ or that $f_2(1, C_0) \to 0$

Leading order Slow Subsystem (SS)

Let

$$S(\tau) = S_0(\tau) + \varepsilon S_1(\tau) + \cdots$$

$$C(\tau) = C_0(\tau) + \varepsilon C_1(\tau) + \cdots$$

— functions of slow time

in the (SS) yields leading order behavior

(6) $$\begin{Vmatrix} \dfrac{dS_0}{d\tau} = f_1(S_0, C_0) \\[2mm] 0 = f_2(S_0, C_0) \end{Vmatrix}$$

Differential Algebraic Equations

Recall that $f_2 = 0 \iff C_0 = H_2(S_0) = \dfrac{S_0}{K_2 + S_0}$

(7) $$\frac{dS_0}{d\tau} = F(S_0) = f_1(S_0, H_2(S_0))$$

Explicitly (7) is

$$\frac{dS_0}{d\tau} = (K_1 - K_2) \cdot H_2(S_0) < 0$$

This is separable and its implicit soln is

$$\boxed{S_0 + K_2 \ln(S_0) - 1 = -(K_2 - K_1) t}$$

Equilibria Stability (FS)

$$\frac{ds}{dt} = \varepsilon f_1(s, c)$$

$$\frac{dc}{dt} = f_2(s, c)$$

Sole equilibria is $P = (0,0)$. Nullclines are

$$f_1 = 0 \qquad c = H_1(s) = \frac{s}{K_1 + s}$$

$$f_2 = 0 \qquad c = H_2(s) = \frac{s}{K_2 + s}$$

Jacobian at $P = (0,0)$

$$D\vec{f}(0,0) = \begin{bmatrix} -\varepsilon & \varepsilon K_1 \\ 1 & -K_2 \end{bmatrix}$$

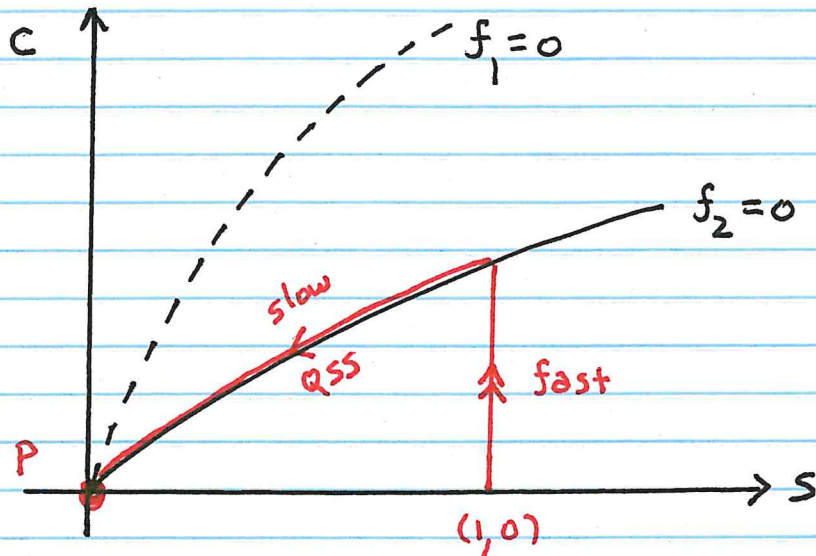From this we see

$$\det D\vec{f} = \varepsilon(K_2 - K_1) > 0$$

$$\operatorname{Tr} D\vec{f} = -(K_2 + \varepsilon) < 0$$

hence P is __stable__.

Summary of Dynamics

(1) Rapidly achieves QSS

(2) Measurable dynamic more likely to only be motion on slow subsystem manifold $f_2 = 0$ or

$$c = \frac{s}{K_2 + s}$$

(3) Continues until substrate depleted

(4) Since $e + c = 1$, $e \to 1$ as $t \to \infty$.

(5) Production rate given by slow subsystem

$$\frac{dp}{dt} = c = \frac{s}{K_2 + s}$$

Production Rate

The dimensionless production rate v is

$$v \equiv \frac{dp}{dt} = \frac{s}{s + k_2}$$

This can be converted back to dimensional form

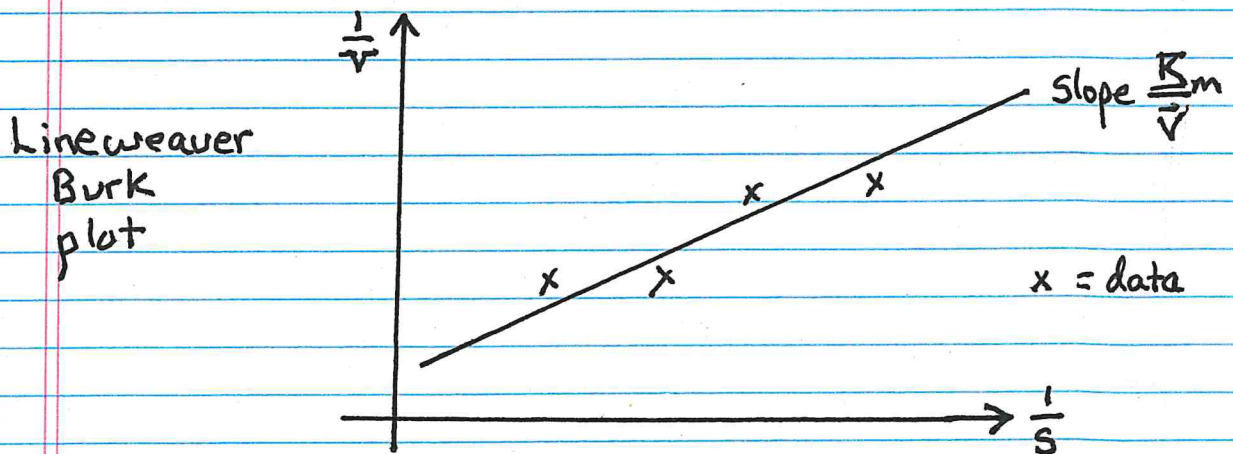$$(1) \qquad V = \frac{dP}{dt} = \frac{\bar{V} S}{K_m + S}$$

where

$$\bar{V} = k_2 E_0 \qquad\qquad K_m = \frac{k_{-1} + k_2}{k_1}$$

Eqn (1) can be re-written

$$\boxed{\frac{1}{V} = \frac{1}{\bar{V}} + \frac{K_m}{\bar{V}} \frac{1}{S}}$$

Measure production rate and S. Use linear regression to find $\bar{V}$ and K_m

Lineweaver
Burk
plot

Slope $\frac{K_m}{\bar{V}}$

x = data

Quick Derivation (Michaelis-Menten)

Suppose you know apriori that E and C
are fast variables then production
rates can be computed directly from
the _dimensional_ equations

$$S' = k_{-1} C - k_1 SE$$

$$E' = (k_{-1} + k_2) C - k_1 SE$$

$$C' = -(k_{-1} + k_2) C + k_1 SE$$

$\left.\begin{array}{c}\end{array}\right\}$ Both zero
when in
QSS

$$P' = k_2 C$$

Noting that the number of receptors
is conserved

$$\boxed{\begin{array}{c}(k_{-1} + k_2) C - k_1 SE = 0 \\[2mm] E + C = E_0\end{array}}$$ QSS

receptors.

These are two eqns for (E, C). Solving these
we get C and E as functions of S:

$$C = \frac{S E_0}{K_m + S}$$

so that

$$\frac{dP}{dt} = k_2 C = \frac{\bar{V} S}{S + K_m}$$

as before.