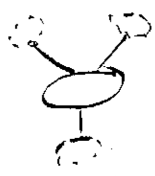
## 6.5: Cooperative phenomena

* multiple binding sites on enzyme: 
* Binding at one site affects binding at others
* Activator substrate: binding at (1) enhances binding at (2), (3) ...
  Inhibitor — " — inhibits.

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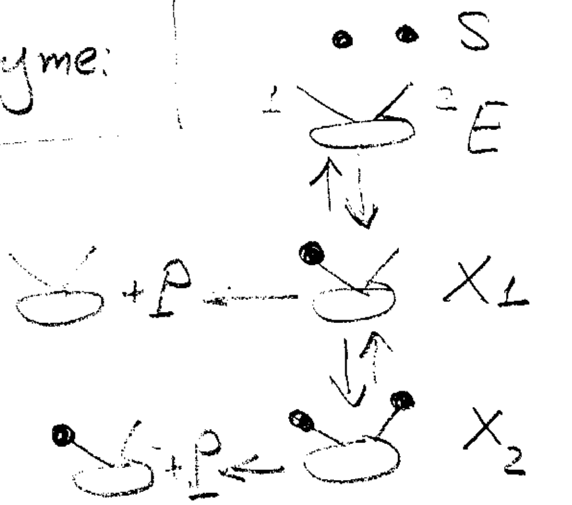
Example: 2 site enzyme:




$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} X_1 \xrightarrow{k_2} E + P$$

$$S + X_1 \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} X_2 \rightarrow X_1 + P$$

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ODS:

$$\begin{cases} \dot{s} = -k_1 se + (k_{-1} - k_3 s)x_1 + k_{-3} x_2 \\ \dot{c}_1 = -k_1 se + (k_{-1} + k_2)x_1 \\ \dot{c}_2 = k_3 s x_1 - (k_{-3} + k_4) x_2 \\ \dot{e} = -k_1 se + (k_{-1} + k_2) x_1 \end{cases}$$

$$\dot{p} = \cdots$$

Mass action: $\boxed{x_1 + x_2 + e = e_0}$

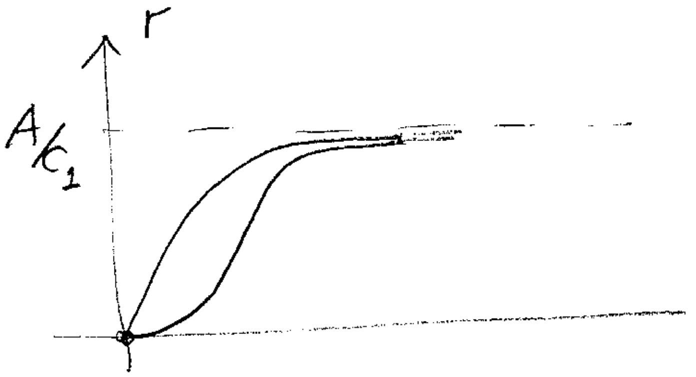
Rescaling: $(x_1, x_2, e) \to \frac{1}{e_0}(x_1, x_2, e) = (v_1, v_2, e)$

$$\begin{cases} \dot{s} = -s + (a_1 + a_2 s) v_1 + a_3 v_2 = f(s, v_1, v_2) \\ \varepsilon \dot{v}_1 = s - (b_1 + b_2 s) v_1 + (b_3 - s) v_2 = g_1(s, v_1, v_2) \leftarrow \text{linear in } v_1 v_2 \\ \varepsilon \dot{v}_2 = c_1 s v_1 - c_2 v_2 = g_2(s, v_1, v_2) \end{cases}$$

Equilibrium, Q-equilibrium

$$\boxed{\dot{s} = -r(s) = -s \frac{A + Bs}{A_1 + B_1 s + C_1 s^2}}$$

Uptake f-n




* Stable equilibrium at 0
* B-dary layer transition (small $\varepsilon > 0$)

Uptake f-n is taken in the form $R(s) = \frac{Q s^n}{K + s^n}$ & depending on $\boxed{n < 1, \; n = 1, \; n > 1}$ have negative, zero, positive cooperation!

$\boxed{n = \# \text{ binding sites on enzyme (?)}}$

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## 6.4. Suicide substrate

1) $$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} X \xrightarrow{k_2} Y \xrightarrow{k_3} E + P$$

$$Y \xrightarrow{k_4} E_i$$

$E_i$ - inactive enzyme

Suicide substrate inactivates enzyme!

$r = \frac{k_3}{k_4}$ - partition ratio for $Y$ pathways.

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2) DS for concentrations

$$\begin{cases} \dot{s} = -k_1 e s + k_{-1} x \\ \dot{x} = k_1 e s - (k_{-1} + k_2) x \\ \dot{y} = k_2 x - (k_3 + k_4) y \\ \dot{e} = -k_1 e s + k_{-1} x + k_3 y \\ \dot{e}_i = k_4 y \end{cases} \Rightarrow$$

Mass conservation (intermediaries + enzymes)

$$\boxed{x + y + e + e_i = e_0}$$

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Reduced 4D system for $(s; x, y, e_i)$

$$\begin{cases} \dot{s} = -k_1 (e_0 - e_i - x - y) s + k_{-1} x \\ \dot{x} = k_1 (\ \ldots\ ) s - (k_{-1} + k_2) x \\ \dot{y} = k_2 x - (k_3 + k_4) y \\ \dot{e}_i = k_4 y \end{cases}$$

# Nondimensionalize

Variables: $S = s/s_0$; $(x, y, e_i) = \dfrac{(x, y, e_i)}{e_0}$;

Parameters:

$$K_m = \frac{k_{-1} + k_2}{k_1} = \frac{\text{removal } (X)}{\text{production } (X)} \quad \text{– Menten}$$

$$\varepsilon = \frac{e_0}{e_0 + K_m} \ll 1 \quad (\text{for } e_0 \ll K_m)$$

D-less:
$$\begin{cases} \tau = k_1 (s_0 + K_m) t \quad \text{– time} \\ \sigma = \dfrac{s_0}{K_m}; \quad \rho = \dfrac{k_{-1}}{k_2}; \quad \psi = \dfrac{k_3 + k_4}{k_{-1} + k_2}; \quad \phi = \dfrac{k_4}{k_{-1} + k_2} < \psi \end{cases}$$

$$(3) \begin{cases} \partial_\tau s = - s\left[(\sigma+1) - \sigma x - (\sigma+1) y - (\sigma+1) e_i\right] + \dfrac{\rho}{1+\rho} x \\ \varepsilon \partial_\tau x = s\left[ \quad \cdot \quad - \quad - \quad - \quad \right] - x \\ \varepsilon \partial_\tau y = \quad \dfrac{\sigma}{(\sigma+1)(\rho+1)} x - \psi y \\ \varepsilon \partial_\tau e_i = \quad \phi y \end{cases}$$

Introduce vector: $X = (x, y, e_i)$ - intermed. + inactive

Write (3) as

$$(4) \begin{cases} \dot{s} = - \boxed{f(X) s} + g(X) \\ \dot{X} = \boxed{f(X) s} \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix} - A \cdot X \end{cases}$$

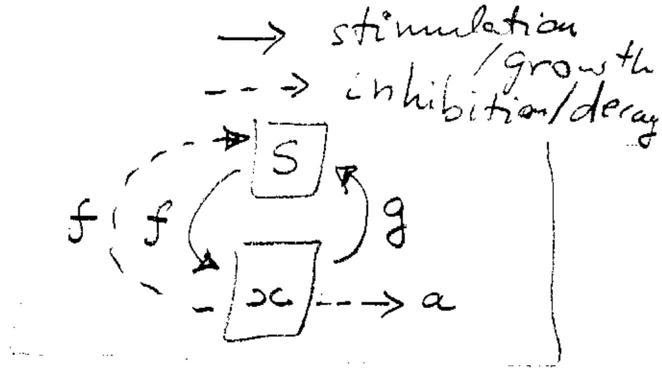
with Linear f-ns

$$f(X) = (\sigma+1)\left[1 - \left(\tfrac{\sigma}{\sigma+1}, 1, 1\right) \cdot X\right]$$

$$g(X) = \left(\tfrac{\rho}{\rho+1}, 0, 0\right) \cdot X$$

Matrix $A = \begin{bmatrix} 1 & 0 & 0 \\ -\sigma/\cdot & \psi & 0 \\ 0 & -\phi & 0 \end{bmatrix}$

3) Reduced 2D version of (4): activator-inhibitor




$$\begin{cases} S = -f(x)S + g(x) \\ \varepsilon\dot{x} = f(x)S - ax \end{cases}$$

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$\boxed{x}$ stimulates growth of $S$ by $g(x)$
& removes w. rate $f(x)$

$\boxed{S}$ stimulates growth of $x$ by $f(x)S \propto S$
+ $x$ decays at rate $a$

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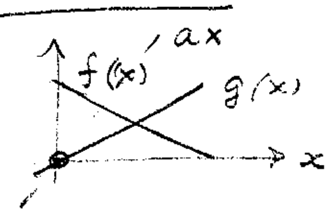
Equilibria: $\boxed{g(x) = ax}$
$x^* = 0;\ S^* = 0$




Jacobian: $J = \begin{bmatrix} -f & -f'S + g' \\ f & f'S - a \end{bmatrix}\Bigg|_{(0,0)} = \begin{bmatrix} -f_0 & g_0' \\ f_0 & -a \end{bmatrix}$

$\operatorname{tr} J < 0$, $\det J = f_0\,(a - g_0') > 0 \Rightarrow$ stable

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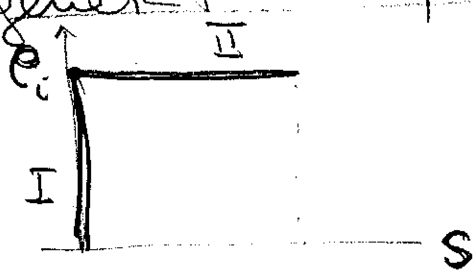
Problem: (a) Show that system (4) has degenerate equilibria: $\boxed{x^* = y^* = 0}$ &




(I) $S = 0;\ 0 \le e_i \le 1$ ← no subst.

(II) $0 \le S \le 1;\ \boxed{e_i = 1}$ ← all enzyme inactivated)

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(b) Show (analytically or numerically) that all solutions converge to one of degenerate equilibria