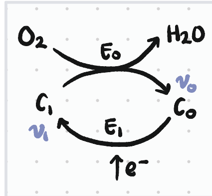
Homework 4.1
Cosubstrate Compensation



Bottom

$$C_0 + E_1 \underset{k^-}{\overset{k^+}{\rightleftharpoons}} [C_0E_1] \xrightarrow{v_b} C_1 + E_1$$

(a) $$\frac{d[E_1]}{dt} = \frac{-d[C_0E_1]}{dt} = -k_+[C_0][E_1] + (k_- + v_b)[C_0E_1]$$

$$\frac{d[C_0]}{dt} = -k_+[C_0][E_1] + k_-[C_0E_1]$$

$$\frac{d[C_1]}{dt} = v[C_0E_1]$$

—inspired by "chapters"—

Define $[E_1]_0 = [E_1] + [C_0E_1]$

Quasi steady: $\frac{d[E_1C_0]}{dt} = 0$

$$\frac{k_+}{k_- + v}\,\frac{[C_0]([E_1]_0 - [C_0E_1])}{[C_0E_1]} = 1$$

$$\frac{[E_1]_0}{[C_0E_1]} = \frac{1}{[C_0]}\underbrace{\left(\frac{k_- + v_b}{k_+}\right)}_{K} + 1$$

$$\frac{[C_0E_1]}{[E_1]_0} = \frac{1}{1 + \frac{1}{[C_0]}K} = \left\{\frac{[C_0]/K}{1 + [C_0]/K}\right\}$$

—inspired by Ed post—

$$\underbrace{\frac{d[E_1]_0}{dt}}_{0} = \underbrace{\frac{d[E_1]}{dt}}_{\therefore\ E_1 \text{ const.}} + \underbrace{\frac{d[C_0E_1]}{dt}}_{QSS = 0}$$

$$\frac{d[C_1]}{dt} = v\frac{k_+}{k_-}[E_1][C_0]$$

Define $k_1 = v_b\frac{k_+}{k_-}[E_1]$

$$v_1 = k_1[C_0]$$

$$v_1 = \frac{d[C_1]}{dt} = v[E_1]_0\,\frac{[C_0]/K}{1 + [C_0]/K}$$

If $[C_0]/K \ll 1$,

$$v_1 = \frac{d[C_1]}{dt} = v[E_1]_0\frac{1}{K}[C_0]$$

Define $k_1 = \frac{v}{K}[E_1]_0$

$$v_1 = k_1[C_0]$$

TOP

$$C_1 + E_0 \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} C_1E_0$$

$$O_2 + C_1E_0 \underset{k_2'}{\overset{k_2}{\rightleftharpoons}} C_1E_0O_2 \xrightarrow{\nu_t} C_0 + E_0 + H_2O$$

$$\frac{d[C_1]}{dt} = -k_1[C_1][E_0] + k_1'[C_1E_0]$$

$$\frac{d[E_0]}{dt} = -k_1[C_1][E_0] + k_1'[C_1E_0] + \nu_t[C_1E_0O_2]$$

$$\frac{d[C_1E_0]}{dt} = k_1[C_1][E_0] - k_1'[C_1E_0] - k_2[C_1E_0][O_2] + k_2'[C_1E_0O_2] = 0$$

QSS

$$\frac{d[C_1E_0O_2]}{dt} = k_2[O_2][C_1E_0] - (k_2' + \nu_t)[C_1E_0O_2] = 0$$

$$\frac{d[C_0]}{dt} = \nu_t[C_1E_0O_2] = f([O_2],[C_1])$$

write $\nu_0 = k_0[C_1]\dfrac{[O_2]/K_0}{1+[O_2]/K_0}$

$$(k_1' + k_2[O_2])[C_1E_0] = k_1[C_1][E_0] + k_2'[C_1E_0O_2]$$

$$(k_2' + \nu)[C_1E_0O_2] = k_2[O_2][C_1E_0] = k_2[O_2]\left(\frac{k_1[C_1][E_0] + k_2'[C_1E_0O_2]}{k_1' + k_2[O_2]}\right)$$

$$k_1'(k_2'+\nu)[C_1E_0O_2] + k_2(k_2'+\nu)[C_1E_0O_2][O_2] = k_1k_2[O_2][C_1][E_0] + k_2k_2'[O_2][C_1E_0O_2]$$

$$\nu[C_1E_0O_2] = \frac{\nu k_1k_2[C_1][E_0][O_2]}{\left(k_1'(k_2'+\nu) + \underbrace{k_2(k_2'+\nu)[O_2] - k_2k_2'[O_2]}_{k_2\nu[O_2]}\right)} = \frac{k_1[C_1][E_0][O_2]}{\dfrac{k_1'(k_2'+\nu)}{k_2\nu} + [O_2]}$$

$$= k_1[E_0][C_1]\frac{\dfrac{k_2\nu}{k_1'(k_2'+\nu)}[O_2]}{1 + \dfrac{k_2\nu}{k_1'(k_2'+\nu)}[O_2]}$$

then $\boxed{\nu_0 = k_0[C_1]\dfrac{[O_2]/K_0}{1+[O_2]/K_0}}$

Define:

$k_0 = k_1[E_0]$

$K_0 = \dfrac{k_1'(k_2+\nu_b)}{k_2\nu_b}$

(b) $C_t = C_0 + C_1$ constant $\frac{d[C_0]}{dt} = \frac{-d[C_1]}{dt}$

$[C_0] = C_t - [C_1]$

$$\frac{dC_1}{dt} = v_1 - v_0 = k_1[C_0] - k_0[C_1]\frac{[O_2]/K_0}{1+[O_2]/K_0}$$

$$= k_1(C_T - [C_1]) - k_0[C_1]\frac{[O_2]/K_0}{1+[O_2]/K_0}$$

$$\boxed{\frac{dC_1}{dt} = k_1 C_T - \left(k_1 + k_0\frac{[O_2]/K_0}{1+[O_2]/K_0}\right)[C_1]}$$

$k_1 = \frac{v_b}{K}E_{10}$ OR $v_b\frac{k_+}{k_-}[E_1]$

$K = \frac{k_- + v}{k_+}$

(c) @ steady state $\frac{dC_1}{dt} = 0$

$$v_0 = \frac{dC_0}{dt} = k_0[C_1]\frac{[O_2]/K_0}{1+[O_2]/K_0} = k_0\frac{k_1 C_T}{k_1 + k_0\frac{[O_2]/K_0}{1+[O_2]/K_0}}\frac{[O_2]/K_0}{1+[O_2]/K_0}$$

$$= \boxed{\frac{k_0 k_1 C_T [O_2]}{k_1 K_0 + (k_0 + k_1)[O_2]}}$$

(d) $\frac{ax}{1+x}$ $x \ll 1$ $v_0 = ax$

$x \gg 1$ $v_0 = a$

Robust in this regime

Rewriting (c)

$$\frac{\frac{k_0 k_1}{k_0+k_1} C_T \frac{k_0+k_1}{k_1 K_0}[O_2]}{1 + \frac{k_0+k_1}{k_1 K_0}[O_2]}$$

$$\therefore \frac{k_0+k_1}{k_1 K_0}[O_2] \gg 1$$

$$[O_2] \gg \frac{k_1 K_0}{k_0 + k_1}$$

look for safest lower bound

Bionumbers:

"O_2[ ] in air-saturated buffers @ 37°C" 200 μM

"O_2[ ] far in air-saturated photosynthetic cell" 230 μM

"O_2[ ] in fetuses pre-birth: 20 mmHg ≈ 1e-3

post-birth: 60 mmHg ≈ 3e-3

$$\left(\frac{k_0}{k_1} + 1\right)1e^{-4} \gg K_0$$

$\boxed{k_0 \gg k_1}$ & K_0 small

Reasonable since v_b & k_2 will be fast relative to k_1

Note too in low $[O_2]$ we lose robustness. Spooky!

intuition: $k_0 \gg k_1$ means fast oxygen consumption relative to the rate C_0 will be depleted again

(e) @ steady state $O_2 \uparrow$

$[O_2]_0$ $[C_1]_0$ $\quad$ $[O_2]_1 \to [C_1]_1 \to$ changes v_0, find time to recover v_0

$$\frac{dc_1}{dt} = k_1 c_T - \left(k_1 + k_0 \frac{[O_2]/K_0}{1+[O_2]/K_0}\right)[C_1]$$

rate in the form $\dot{y} + by = a$ where $y = [C_1]$, $a = k_1 C_T$, $b_1 = k_1 + k_0 \frac{[O_2]_1/K_0}{1+[O_2]_1/K_0}$

inhomogeneous first-order ODE solution of form:

$$y = \frac{a}{b} + \left([C_1]_0 - \frac{a}{b}\right)e^{-bt}$$

$$y = \frac{a}{b}\left(1 + \left(\frac{b}{a}[C_1]_0 - 1\right)e^{-bt}\right)$$

$$c_1(t_1) = \frac{a}{b_1}\left(1 + \left(\frac{b_1}{a}[C_1]_0 - 1\right)e^{-bt}\right)$$

Response time seems to scale with a/b_1 but let's explicitly solve for fun :)

$$v_{0\,step} = [C_1]\underbrace{k_0 \frac{[O_2]/K_0}{1+[O_2]/K_0}}_{b_0 - k_1}$$

write b_0 functional form $b_0 = k_1 + k_0 \frac{[O_2]_0/K_0}{1+[O_2]_0/K_0}$

$$= \frac{a}{b_1}\left(1 + \left(\frac{b_1}{a}[C_1]_0 - 1\right)e^{-b_1 t^*}\right)(b_1 - k_1) = [C_1]_0 (b_0 - k_1)$$

* solve for t when $v_{0\,step}$ reaches v_0

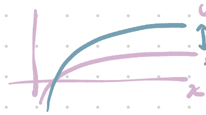
$$e^{-b_1 t} = \frac{\frac{b_1}{a}[C_1]_0 \frac{(b_0 - k_1)}{(b_1 - k_1)} - 1}{\frac{b_1}{a}[C_1]_0 - 1}$$

$$t = \frac{1}{b_1} \ln \underbrace{\left(\frac{\frac{b_1}{a}[C_1]_0 - 1}{\frac{b_1}{a}[C_1]_0 \frac{(b_0 - k_1)}{(b_1 - k_1)} - 1}\right)}_{\text{This term is effectively } \ln(1+\epsilon)}$$

< 1 since oxygen stepping up

This term is effectively $\ln(1+\epsilon)$ which graphically looks like

where $x = \frac{b_1}{a}[C_1]_0$



the blue term

$$\frac{b_0 - k_1}{b_1 - k_1} = \frac{\frac{[O_2]_0/K_0}{1+[O_2]_0/K_0}}{\frac{[O_2]_1/K_0}{1+[O_2]_1/K_0}}$$

is dependent on step size but this ratio of sigmoids gets logged, a heavily dampening function

$\therefore$ the predominant term of consideration is $\frac{1}{b_1} = \frac{1}{k_1 + k_0 \frac{[O_2]_1/K_0}{1+[O_2]_1/K_0}}$

This term is robust to changes in $[O_2]$ when $\boxed{k_1 \gg k_0}$

the production of C_1 (bottom) scales much faster than the top reaction. This matches our intuition, this is the regime where C_1 does not react quickly enough to sense dramatic changes in O_2.

(f) From part (c) $v_0 = \frac{k_0 k_1 C_T [O_2]}{k_1 K_0 + (k_0 + k_1)[O_2]}$

The fastest rate is when $[O_2]$ high. Thus

$$v_{0_{max}} = \frac{k_0 k_1}{k_0 + k_1} C_T$$

Solve for K_m:

$$\frac{1}{2} v_{0max} = \frac{\cancel{k_0 k_1 C_T} K_m}{k_1 K_0 + (k_0 + k_1) K_m} = \frac{1}{\frac{k_1 K_0}{K_m} + (k_0 + k_1)}$$

$$\downarrow$$

$$\frac{1}{2} \frac{\cancel{k_0 k_1}}{k_0 + k_1} \cancel{C_T} \qquad 2(k_0 + k_1) - (k_0 + k_1) = \frac{k_1 K_0}{K_m}$$

$$K_m = \frac{k_1 K_0}{k_0 + k_1}$$

Robustness from part (d) $k_0 >> k_1$

$$= \frac{k_1}{k_0} K_0$$

Recall $v_1 = k_1 [C_0]$

$$= \frac{v_1 K_0}{k_0 [C_0]}$$

We are indeed linear with v_1 & inverse in k_0.

What are the chance[s]...?