Question 2

a)

S.S. balance so

$$\left.\frac{dL}{dt}\right|_{z=z>0} = 0 = \underbrace{\underbrace{K_m(z)\left[L_b - L_c(z)\right]}_{\left(\frac{m}{s}\right)\left(\frac{\#}{m^3}\right) \to \frac{\#}{s\,m^2}}\underbrace{\left(\frac{1}{\text{density of cells}}\right)}_{\frac{m^2}{cell}}}_{\frac{\#}{sec \cdot cell}} + \underbrace{q}_{\frac{\#}{sec \cdot cell}} + \underbrace{K_r R_s^*}_{\left(\frac{1}{s}\right)\left(\frac{\#}{cell}\right) \to \frac{\#}{sec \cdot cell}} - \underbrace{K_f R_s L_c(z)}_{\left(\frac{m^3}{\# sec}\right)\left(\frac{\#}{cell}\right)\left(\frac{\#}{m^3}\right) \to \frac{\#}{sec \cdot cell}}$$

Should be $\frac{1}{\# cells}\frac{dL}{dt}$ but

(The whole thing should be multiplied by # of cells but it just divides out so I didn't include it)

density of cells (@ $t=0$) $= n_c$ → because we are only interested in the initial mitotic response I'm assuming density of cells $= n_c$ (constant)

from Knauer

$$\frac{\text{Mitotic rate}}{\text{max rate}} = \gamma \cdot R^*_{Total} = \gamma\left[\frac{1}{k_e^*} + \frac{1}{k_{deg}}\right]\left[\frac{K_{ss}L}{1+K_{ss}L}\right]V_s$$

where

$$K_{ss} = \frac{k_e^* k_f}{k_e(k_r + k_e^*)}$$

so

$$0 = \frac{K_m L_b}{n_c} - \frac{K_m L_c}{n_c} + q + K_r R_s^* - K_f R_s L_c$$

$$L_c\left[\frac{K_m}{n_c} + K_f R_s\right] = \frac{K_m L_b}{n_c} + q + K_r R_s^*$$

$$L_c(z) = \frac{\dfrac{K_m(z) L_b + q n_c + K_r R_s^* n_c}{n_c}}{\dfrac{K_m + K_f R_s n_c}{n_c}}$$

↓

question 2) continued

a)

$$L_c(z) = \left(\frac{k_m(z) L_b + q n_c + k_r R_s^* n_c}{n_c}\right)\left(\frac{n_c}{k_m(z) + k_f R_s n_c}\right)$$

$$\boxed{L_c(z) = \left[\frac{k_m(z) L_b + q n_c + k_r R_s^* n_c}{k_m(z) + k_f R_s n_c}\right]}$$

unit check

$$\frac{\#}{m^3} = \frac{\left(\frac{m}{s}\right)\left(\frac{\#}{m^3}\right) + \left(\frac{\#}{s \cdot cell}\right)\left(\frac{cell}{m^2}\right) + \left(\frac{1}{s}\right)\left(\frac{\#}{cell}\right)\left(\frac{cell}{m^2}\right)}{\left(\frac{m}{s}\right) + \left(\frac{m^3}{\# s}\right)\left(\frac{\#}{cell}\right)\left(\frac{cell}{m^2}\right)}$$

$$\frac{\#}{m^3} = \frac{\left(\frac{\#}{s\,m^2}\right) + \left(\frac{\#}{s\,m^2}\right) + \left(\frac{\#}{s\,m^2}\right)}{\left(\frac{m}{s}\right) + \left(\frac{m}{s}\right)}$$

$$\frac{\#}{m^3} = \left(\frac{\#}{s\,m^2}\right)\left(\frac{s}{m}\right) = \frac{\#}{m^3}$$

B)

Transport Limited $\left(k_m \text{ is very small}\right)$: $\boxed{L_c(z) = \frac{q n_c + k_r R_s^* n_c}{k_f R_s n_c} = \frac{q + k_r R^*}{k_f R_s}}$

Binding Limited $\left(k_m \text{ is very large}\right)$: $\boxed{L_c(z) = \frac{k_m(z) L_b}{k_m(z)} = L_b}$

$\downarrow$

B)

Transport Limited explanation: Transport is slow ∴ the mass transfer between the boundary layers term is not present. ∴ the only thing increasing L_c is the generation (q) and the unbinding of previous ligand → $(K_r R_s^*)$. For the same reason the only consumption is from the ligand binding $(K_f R_s)$. Because the rate of binding is a function of ligand the expression for L_c is a ratio rather than summation.

Binding Limited explanation: Binding is slow ∴ comparatively not much ligand is bound and ∴ there is not a great impact on L_c from unbinding either. And because transport is relatively fast $L_c = L_b$ as any difference between the two (i.e. from q) is quickly redistributed evenly.

Question 2 continued

C from Knauer

$$\frac{\text{Mitotic rate}}{\text{max rate}} = \gamma \cdot R^*_{TOTAL} = \gamma \left[\frac{1}{k_e^*} + \frac{1}{k_{deg}}\right]\left[\frac{K_{ss} L_c(z)}{1+K_{ss}L_c(z)}\right] V_s$$

where $K_{ss} = \frac{k_e^* k_f}{k_e(k_r + k_e^*)}$

and γ = mitogenic signal
↳ (slope of Knauer graph)

From A)

$$L_c(z) = \frac{k_m(z) L_b + q n_c + k_r R_s^* n_c}{k_m(z) + k_f R_s n_c}$$

in the limit of low $[L] \rightarrow L_c K_{ss} \ll 1$, $L_b = 0$

gives: $$L_c(z) = \frac{q n_c + k_r R_s^* n_c}{k_m(z) + k_f R_s n_c}$$

$$\frac{\text{Mitotic Rate}}{\text{Max Rate}} = \gamma \boxed{\left[\frac{1}{k_e^*} + \frac{1}{k_{deg}}\right]\left[K_{ss} V_s\right]\left[\frac{q n_c + k_r R_s^* n_c}{k_m(z) + k_f R_s n_c}\right]}$$

Box $= R^*_{TOTAL}$

$$\frac{\text{Mitotic Rate}}{\text{max Rate}} = \rightarrow \gamma R^*_{TOTAL}$$

issue R_s^*, R_s

question 2 continued

d) given

$K_e = 10^{-4}\ (s^{-1})$, $K_e^* = 5\cdot10^{-3}\ (s^{-1})$

$K_f = 3.1\cdot10^{6}\ (M^{-1}s^{-1}) = 5.14\cdot10^{-21}\ (m^3\, s^{-1})$

$K_r = 2.5\cdot10^{-2}\ (s^{-1})$, $K_{deg} = 8\cdot10^{-4}\ (s^{-1})$

$V_s = 18\ (s^{-1}\,cell^{-1})$, $q = 10^3\ (\#\ cell^{-1}s^{-1})$

$n_c = 3\cdot10^{8}\ (cell\cdot m^{-2})$

$$Sh_z = \frac{K_m(z)}{D_L/z} = \left(\frac{\dot{\gamma} z^2}{D_L}\right)^{1/3}$$

$$\swarrow$$

$$K_m(z) = \left(\frac{\dot{\gamma}^{1/3} z^{2/3}}{D_L^{1/3}}\right)\left(\frac{D_L}{z}\right)$$

$$\boxed{K_m(z) = \frac{\dot{\gamma}^{1/3} D_L^{2/3}}{z^{1/3}} = \left(\frac{\dot{\gamma} D_L^2}{z}\right)^{1/3}}$$

$\dot{\gamma} = 10^2\ (s^{-1})$, $D_L = 10^{-10}\ (m^2 s^{-1})$