Question 2

a)

S.S. balance so

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

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

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

$\boxed{C}$ from Knauer

$$\frac{\text{Mitotic rate}}{\text{max rate}} = \gamma \cdot R^*_{TOTAL}$$

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

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] → $L_c K_{ss} \ll 1$, $L_b = 0$

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

@ S.S. $V_s = K_e R_s + K_e R_s^*$ (1)

from notes and HWs

$$\frac{dR_s^*}{dt} = K_f L_c R_s - K_r R_s^* - K_e^* R_s^* \quad (2)$$

rearranging (1)

$$R_s = \frac{V_s - K_e R_s^*}{K_e} \quad (3)$$

from A) with $L_b = 0$

$$L_c = \frac{n_c (q + K_r R_s^*)}{K_m + K_f R_s n_c} \quad (4)$$

subbing (4) into (2)

$$-K_f R_s (n_c)\left(\frac{q + K_r R_s^*}{K_m + K_f R_s n_c}\right) = -K_r R_s^* - K_e^* R_s^*$$

now subbing in (3)

$$-\frac{K_f n_c}{K_e}(V_s - K_e R_s^*)\left(\frac{q + K_r R_s^*}{K_m + K_f n_c\left(\frac{V_s - K_e R_s^*}{K_e}\right)}\right) = (-K_r - K_e^*) R_s^*$$

$$\left(\frac{K_f V_s}{K_e(K_r + K_e^*)} - \frac{K_f K_e R_s^*}{K_e(K_r + K_e^*)}\right)\underbrace{\left(\frac{(q + K_r R_s^*) n_c}{K_m + K_f n_c\left(\frac{V_s - K_e R_s^*}{K_e}\right)}\right)}_{L_c} = R_s^*$$

$$\left(\frac{K_f V_s}{K_e(K_r + K_e^*)} - K_{ss} R_s^*\right)(L_c) = R_s^*$$

↓

$$\left(\frac{K_{ss}}{K_e} V_s - K_{ss} R_s^*\right) L_c = R_s^*$$

$$\frac{K_{ss} L_c}{K_e R_s^*} V_s - K_{ss} L_c = 1$$

$$\frac{K_{ss} L_c}{K_e R_s^*} V_s = 1 + K_{ss} L_c$$

as $K_{ss} L_c \ll 1$

$$\frac{K_{ss} L_c}{K_e R_s^*} V_s = 1$$

$$R_s^* = \left(\frac{K_{ss}}{K_e} V_s\right)\left(\frac{n_c (q + K_r R_s^*)}{K_m + K_f n_c \left(\frac{V_s - K_e R_s^*}{K_e}\right)}\right)$$

$$R_s^* = \frac{K_{ss} V_s}{K_e}\left(\frac{n_c K_e (q + K_r R_s^*)}{K_m K_e + K_f n_c V_s - K_f n_c K_e R_s^*}\right)$$

$$R_s^* = \frac{(K_{ss} V_s n_c K_e q) + (K_{ss} V_s n_c K_e K_r) R_s^*}{K_m K_e + K_f n_c V_s - K_f n_c K_e R_s^*}$$

$$-R_s^{*2}(K_f n_c K_e) + (K_m K_e + K_f n_c V_s) R_s^* = (K_{ss} V_s n_c K_e q) + (K_{ss} V_s n_c K_e K_r) R_s^*$$

$$R_s^{*2}\underbrace{(K_f n_c K_e)}_{a} + \underbrace{(K_{ss} V_s n_c K_e K_r - K_m K_e - K_f n_c V_s)}_{b} R_s^* + \underbrace{(K_{ss} V_s n_c K_e q)}_{c} = 0$$

$a = k_f n_c k_e$, $b = (k_{ss} v_s n_c k_e k_{tr} - k_m k_e - k_f n_c k_s)$, $c = k_{ss} v_s n_c k_{eq}$

$$R_s^* = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

(take the positive root)

from notes: $\frac{\partial R_i^*}{dt} = k_e^* R_s^* - k_{deg} R_i^*$

@ SS. $\boxed{R_i^* = \frac{k_e^*}{k_{deg}} R_s^*}$

$R^*_{TOTAL} = R_i^* + R_s^*$

as shown below

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

for D I didn't know γ, mitotic signal,

so I just plotted R^*_{TOTAL} vs z.

question 2 continued

d) given

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

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

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

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

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

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

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

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

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

All the calculations were done in the Excel file.

Calculated			
Kss	8.56667E-18	m3	
(1/Ke* + 1/kdeg)*Kss*Vs	2.2359E-13	m3/cell	
Mitogenic Signal	?		

I didn't know what to put for the mitogenic signal so I just plotted R*Total vs Z. Also This is what I got from my hand derevation.