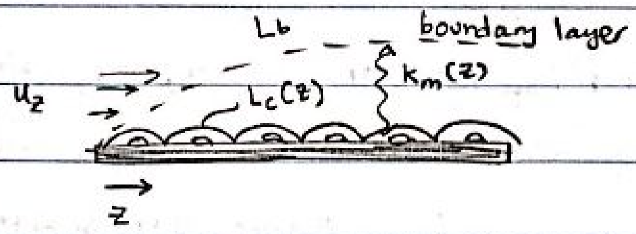
2.



u_z [=] $\frac{1}{s}$

$k_m(z)$ [=] $\frac{m}{s}$

L_b [=] $\frac{\#}{m^3}$

R_s^* [=] $\frac{\#}{cell}$ [=] conc bound surface receptor

q [=] $\frac{\#}{s \cdot cell}$

R_s [=] $\frac{\#}{cell}$ [=] conc unbound surface receptor

η_{cell} [=] $\frac{cell}{m^2}$

k_f [=] $\frac{m^3}{\# \cdot s}$, k_r [=] $\frac{1}{s}$ } rates

$k_r R_s^*$ [=] $\frac{\#}{cell \cdot s}$

q [=] $\frac{\#}{s \cdot cell}$ [=] secretion rate of EGF

η_c [=] initial density of cells

L_b [=] bulk ligand conc [=] $\frac{\#}{m^3}$

$L_c(z)$ [=] volumetric ligand conc at cell surface [=] $\frac{\#}{m^3}$

$k_m(z)$ [=] local mass transfer coefficient [=] $\frac{m}{s}$

rate of EGF transport from bulk to monolayer: $k_m(z)[L_b - L_c(z)]$

(a). S.S. species balance for EGF

$$\frac{\partial R_s}{\partial t} = -k_f R_s(L_c(z)) + k_r R_s^*$$

mass balances

$$\frac{\partial R_s^*}{\partial t} = k_f R_s(L_c(z)) - k_r R_s^*$$

$$\frac{\partial L}{\partial t} = q + \frac{k_m(z)[L_b - L_c(z)]}{\eta_c} - k_f R_s L_c(z) + k_r R_s^*$$

$$0 = q + \frac{k_m(z)[L_b - L_c(z)]}{n_c} - k_f R_s L_c(z) + k_r R_s^*$$

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

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

(b) Transport limited ($k_m << 1$): $L_c(z) = \frac{q + k_r R_s^*}{k_f R_s}$

Binding limited ($k_m >> 1$): $L_c(z) = L_b$

In the transport limited regime only the EGF concentration on the cell surface and cell activities influence $L_c(z)$.

Binding limited regime - $L_c(z)$, the EGF concentration as a function of z is only influenced by bulk movement of EGF.

2.

(c) $R_s^T = R_s + R_s^*$ $\qquad$ $L_c k_{ss} << 1$, $L_b = 0$

$$\frac{\partial R_s}{\partial t} = -k_f L_c(z) R_s + k_r R_s^* - k_e R_s + V_s = 0$$

$$\frac{\partial R_s^*}{\partial t} = k_f L_c(z) R_s - k_r R_s^* - k_e^* R_s^* = 0$$

$$-R_s(k_f L_c + k_e) + k_r R_s^* + V_s = 0 \Rightarrow$$

$$\frac{k_r R_s^* + V_s}{k_f L_c + k_e} = R_s$$

$$R_s^*(k_r + k_e^*) = k_f L_c R_s \Rightarrow R_s^* = \frac{k_f L_c R_s}{k_r + R}$$

$$R_s = \frac{(k_e^* + k_r) V_s}{k_e(k_e^* + k_r) + k_e^* k_f L_c} \qquad R_s^* = \frac{k_f L_c V_s}{k_e(k_e^* + k_r) + k_e^* k_f L_c}$$

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

For $L_c k_{ss} << 1$,

$$R_T^* = R_s^* + R_i^* = \left(\frac{1}{k_e^*} + \frac{1}{k_{deg}}\right)\left(\frac{k_{ss} L}{1 + k_{ss} L}\right) V_s$$

$$\rightarrow R_T(z) = \left(\frac{1}{k_e^*} + \frac{1}{k_{deg}}\right)\left(\frac{k_{ss} L_c(z)}{1}\right) V_s$$

With $L_b = 0$

$$\rightarrow R_T^*(z) = \left(k_{ss}\left(\frac{n_c q + k_r n_c R_s^*}{k_m + k_f n_c R_s}\right) V_s \left(\frac{1}{k_e^*} + \frac{1}{k_{deg}}\right)\right)$$

where $R_s^* = \dfrac{k_e k_m (k_e^* + k_r) + k_e^* k_f n_c (q + V_s) + \sqrt{(k_e k_m (k_e^* + k_r) + k_e^* k_f n_c (q - V_s))^2 + 4 k_e k_e^* k_f k_m (k_e^* + k_r) n_c V_s}}{2 k_e^{*2} k_f k_m}$

$$R_s = \frac{k_e k_m (k_e^* + k_r) + k_e^* k_f n_c (q - V_s) + \sqrt{(k_e k_m (k_e^* + k_r) + k_e^* k_f n_c (q - V_s))^2 + 4 k_e k_e^* k_f k_m (k_e^* + k_r) n_c V_s}}{2 k_e k_e^* k_f n_c}$$

(d) $\dfrac{\text{mitotic rate}}{\text{max rate}} = \gamma \cdot R^*_{Total}$ $\qquad$ mitotic rate = (max rate) γR^*_{Total}

$$\gamma = \frac{\Delta \text{Normalized mitotic rate \%}}{\Delta R_{Total} \times 10^{-3}} \cdot (R^*_{Tot})$$

$$R_T^{*,max} = \left(\frac{1}{k_e^*} + \frac{1}{k_{deg}}\right) V_s = 202500 \qquad (\text{when } k_{ss} L >> 1)$$

$$\frac{1}{s^{-1}} \cdot (s) \frac{1}{\text{cell} \cdot s} = \frac{\#}{\text{cell}}$$

does not apply when $L_{ss} L << 1$

$\therefore$ mitotic rate is proportional to R_T^* so a plot of mitotic rate captures the mitotic activity.

(a)

Solving the differential for Lc at steady state gives the following expression:

In[1]:=
```
Solve[0 == q + ((km * (Lb - Lc)) / nc) - kf * Rs * Lc + kr * Rsst, Lc] // FullSimplify
```

Out[1]= $\left\{\left\{Lc \to \frac{km\, Lb + nc\, q + kr\, nc\, Rsst}{km + kf\, nc\, Rs}\right\}\right\}$

(b)

In the transport limited regime, the following expression results. This is because the EGF concentration on the cell surface is effected by the binding and unbinding of ligand to the receptor and the rate of production, not the bulk concentration of ligand.

In[2]:= $\text{Limit}\left[\frac{km\, Lb + nc\, q + kr\, nc\, Rsst}{km + kf\, nc\, Rs}, km \to 0\right]$ // FullSimplify

Out[2]= $\frac{q + kr\, Rsst}{kf\, Rs}$

In the binding limited regime, the EGF concentration at the cell surface is affected by the bulk concentration of ligand.

In[3]:= $\text{Limit}\left[\frac{km\, Lb + nc\, q + kr\, nc\, Rsst}{km + kf\, nc\, Rs}, km \to \text{Infinity}\right]$

Out[3]= Lb

(c)

Solve for the the active and inactive surface receptor concentration in terms of km(z) and substitute into the function for L.

In[4]:=
```
Solve[{0 == -kf * Lc * Rs + kr * Rsst - ke * Rs + vs,
   0 == kf * Lc * Rs - kr * Rsst - kest * Rsst, 0 == kest * Rsst - kdeg * Rist,
   0 == ke * Rs - kdeg * Ri, 0 == q + ((km * (-Lc)) / nc) - kf * Rs * Lc + kr * Rsst},
  {Ri, Rs, Rist, Rsst, Lc}] // FullSimplify
```

Out[4]= $\left\{\left\{Ri \to -\frac{1}{2\, kdeg\, kest\, kf\, nc}\left(ke\, km\, (kest + kr) + kest\, kf\, nc\, (q - vs) + \sqrt{(ke\, km\, (kest + kr) + kest\, kf\, nc\, (q - vs))^2 + 4\, ke\, kest\, kf\, km\, (kest + kr)\, nc\, vs}\right),\right.\right.$

$Rs \to -\frac{1}{2\, ke\, kest\, kf\, nc}\left(ke\, km\, (kest + kr) + kest\, kf\, nc\, (q - vs) + \sqrt{(ke\, km\, (kest + kr) + kest\, kf\, nc\, (q - vs))^2 + 4\, ke\, kest\, kf\, km\, (kest + kr)\, nc\, vs}\right),$

$Rist \to \frac{1}{2\, kdeg\, kest\, kf\, nc}\left(ke\, km\, (kest + kr) + kest\, kf\, nc\, (q + vs) + \right.$

$$\sqrt{\left(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q-\text{vs}\right)\right)^2+4\,\text{ke kest kf km}\left(\text{kest}+\text{kr}\right)\text{nc vs}}\Bigg),$$

$$\text{Rsst}\to\frac{1}{2\,\text{kest}^2\,\text{kf nc}}\Bigg(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q+\text{vs}\right)+$$

$$\sqrt{\left(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q-\text{vs}\right)\right)^2+4\,\text{ke kest kf km}\left(\text{kest}+\text{kr}\right)\text{nc vs}}\Bigg),$$

$$\text{Lc}\to-\frac{1}{2\,\text{kest kf km}}\Bigg(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(-q+\text{vs}\right)+$$

$$\sqrt{\left(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q-\text{vs}\right)\right)^2+4\,\text{ke kest kf km}\left(\text{kest}+\text{kr}\right)\text{nc vs}}\Bigg)\Big\},$$

$$\Big\{\text{Ri}\to\frac{1}{2\,\text{kdeg kest kf nc}}\Bigg(-\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(-q+\text{vs}\right)+$$

$$\sqrt{\left(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q-\text{vs}\right)\right)^2+4\,\text{ke kest kf km}\left(\text{kest}+\text{kr}\right)\text{nc vs}}\Bigg),$$

$$\text{Rs}\to\frac{1}{2\,\text{ke kest kf nc}}\Bigg(-\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(-q+\text{vs}\right)+$$

$$\sqrt{\left(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q-\text{vs}\right)\right)^2+4\,\text{ke kest kf km}\left(\text{kest}+\text{kr}\right)\text{nc vs}}\Bigg),$$

$$\text{Rist}\to\frac{1}{2\,\text{kdeg kest kf nc}}\Bigg(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q+\text{vs}\right)-$$

$$\sqrt{\left(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q-\text{vs}\right)\right)^2+4\,\text{ke kest kf km}\left(\text{kest}+\text{kr}\right)\text{nc vs}}\Bigg),$$

$$\text{Rsst}\to\frac{1}{2\,\text{kest}^2\,\text{kf nc}}\Bigg(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q+\text{vs}\right)-$$

$$\sqrt{\left(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q-\text{vs}\right)\right)^2+4\,\text{ke kest kf km}\left(\text{kest}+\text{kr}\right)\text{nc vs}}\Bigg),$$

$$\text{Lc}\to\frac{1}{2\,\text{kest kf km}}\Bigg(-\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q-\text{vs}\right)+$$

$$\sqrt{\left(\text{ke km}\left(\text{kest}+\text{kr}\right)+\text{kest kf nc}\left(q-\text{vs}\right)\right)^2+4\,\text{ke kest kf km}\left(\text{kest}+\text{kr}\right)\text{nc vs}}\Bigg)\Big\}\Big\}$$

In[5]:=
```
ke = 10^-4;
kest = 0.005;
kf  = 5.14 * 10^-21;
kr = 0.025;
kdeg = 0.0008;
vs = 18;
q = 1000;
nc = 3 * 10^8;
```

In[13]:=
```
Kss  =  (kest * kf) / (ke * (kr + kest))
```

Out[13]= 8.56667×10^{-18}

The total active receptor concentration is analyzed in the limit where Ls*Kss << 1. The total active receptor concentration formula is (7) from the ultrasensitivity lecture notes.

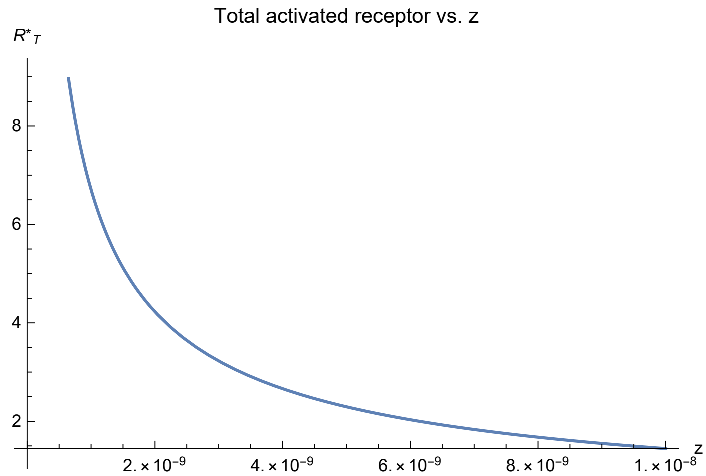
In[14]:=
```
km[z_] := ((100 * z^2) / (10^-10))^(1/3)
```

In[15]:=
$$\text{RTfunc}[z\_] = ((1/\text{kdeg}) + (1/\text{kest})) * \text{vs} * \text{Kss} * \left(\left(\text{nc q} + \text{kr nc}\left(\frac{1}{2\,\text{kest}^2\,\text{kf nc}}\left(\text{ke km}[z]\,(\text{kest}+\text{kr}) + \text{kest kf nc}\,(q+\text{vs}) - \sqrt{(\text{ke km}[z]\,(\text{kest}+\text{kr}) + \text{kest kf nc}\,(q-\text{vs}))^2 + 4\,\text{ke kest kf km}[z]\,(\text{kest}+\text{kr})\,\text{nc vs}}\right)\right)\right) \middle/ \left(\text{km}[z] + \text{kf nc}\left(\frac{1}{2\,\text{ke kest kf nc}}\left(-\text{ke km}[z]\,(\text{kest}+\text{kr}) + \text{kest kf nc}\,(-q+\text{vs}) + \sqrt{(\text{ke km}[z]\,(\text{kest}+\text{kr}) + \text{kest kf nc}\,(q-\text{vs}))^2 + 4\,\text{ke kest kf km}[z]\,(\text{kest}+\text{kr})\,\text{nc vs}}\right)\right)\right)\right)$$

Out[15]=
$$\left(2.2359\times10^{-13}\left(300\,000\,000\,000 + 9.72763\times10^{22}\left(7.84878\times10^{-12} + 0.03\,(z^2)^{1/3} - \sqrt{1.66536\times10^{-14}\,(z^2)^{1/3} + \left(7.57122\times10^{-12} + 0.03\,(z^2)^{1/3}\right)^2}\right)\right)\right) \middle/ \left(10\,000\,(z^2)^{1/3} + 1.\times10^{6}\left(-7.57122\times10^{-12} - 0.03\,(z^2)^{1/3} + \sqrt{1.66536\times10^{-14}\,(z^2)^{1/3} + \left(7.57122\times10^{-12} + 0.03\,(z^2)^{1/3}\right)^2}\right)\right)$$

In[22]:=
```
p1 = Plot[RTfunc[z], {z, 0, 0.00000001},
  AxesLabel → {"z", "R*T"}, PlotLabel → "Total activated receptor vs. z"]
```

Out[22]=



Looking at the plot on a nanometer scale, there appears to be a decrease in total activated receptor concentration as z increases. The normalized mitotic rate is equal to the the total activated receptor concentration multiplied by γ, the intrinsic mitogenic signal generation. Therefore the plot clearly shows the mitotic activity decreases as a function of z, since it is proportional to the active receptor concentration times a factor of γ.