

## 1. Lateral Inhibition, Notch-Delta Signalling

- a)  $N_x$ : active notch in cell  $x$   
 $D_x$ : active Delta in cell  $x$   
 $F$ : activation function  
 $G$ : inhibition function  
 $\gamma$ : degradation constant

$$\begin{aligned}\frac{dN_1}{dt} &= F(D_2) - \gamma_N N_1, \\ \frac{dN_2}{dt} &= F(D_1) - \gamma_N N_2, \\ \frac{dD_1}{dt} &= G(N_2) - \gamma_D D_1, \\ \frac{dD_2}{dt} &= G(N_1) - \gamma_D D_2\end{aligned}$$

make dimless with  
 $\tau = \gamma_D t$   
(different from  
lecture procedure)

$$v = \frac{\gamma_D}{\gamma_N}$$

$$f = \frac{F}{\gamma_N}$$

$$g = \frac{G}{\gamma_D}$$

$$\tau = \gamma_D t$$

$$\frac{dN_1}{d\tau} = \frac{1}{v} (f(D_2) - N_1)$$

$$\frac{dN_2}{d\tau} = \frac{1}{v} (f(D_1) - N_2)$$

$$\frac{dD_1}{d\tau} = g(N_2) - D_1$$

$$\frac{dD_2}{d\tau} = g(N_1) - D_2$$

if  $v = \frac{\gamma_D}{\gamma_N} \ll 1$ ,

$$\begin{aligned}v \frac{dN_1}{d\tau} &= f(D_2) - N_1 \rightarrow 0 & \left( \frac{dN_1}{d\tau} \approx 0 \right) \\ v \frac{dN_2}{d\tau} &= f(D_1) - N_2 \rightarrow 0 & \left( \frac{dN_2}{d\tau} \approx 0 \right)\end{aligned}$$

Active Notch in cells 1 + 2 reaches a steady state

RETURN TO EQUATIONS FROM CLASS, where  $\tau = \gamma_D t$

$$\begin{aligned}\frac{dN_1}{d\tau} &= f(D_2) - N_1 = 0 \Rightarrow N_1 = f(D_2) \\ \frac{dN_2}{d\tau} &= f(D_1) - N_2 = 0 \Rightarrow N_2 = f(D_1) \\ \frac{dD_1}{d\tau} &= v(g(N_2) - D_1) \\ \frac{dD_2}{d\tau} &= v(g(N_1) - D_2)\end{aligned}$$

$$\boxed{\begin{aligned}\frac{dD_1}{d\tau} &= v(g(f(D_2)) - D_1) \\ \frac{dD_2}{d\tau} &= v(g(f(D_1)) - D_2)\end{aligned}}$$

b) FROM MAY 7 LECTURE:

$$f(D') = \frac{F(D')}{\gamma_N} = \frac{D'^2}{0.1 + D'^2}$$

$$g(N) = \frac{G(N)}{\gamma_D} = \frac{1}{1 + 10N^2}$$

for nullclines:

$$\frac{dD_1}{d\tau} = 0 = g(f(D_2) - D_1) \Rightarrow D_1 = g(f(D_2)) = g\left(\frac{D_2^2}{0.1 + D_2^2}\right) = \frac{1}{1 + 10\left(\frac{D_2^2}{0.1 + D_2^2}\right)^2}$$

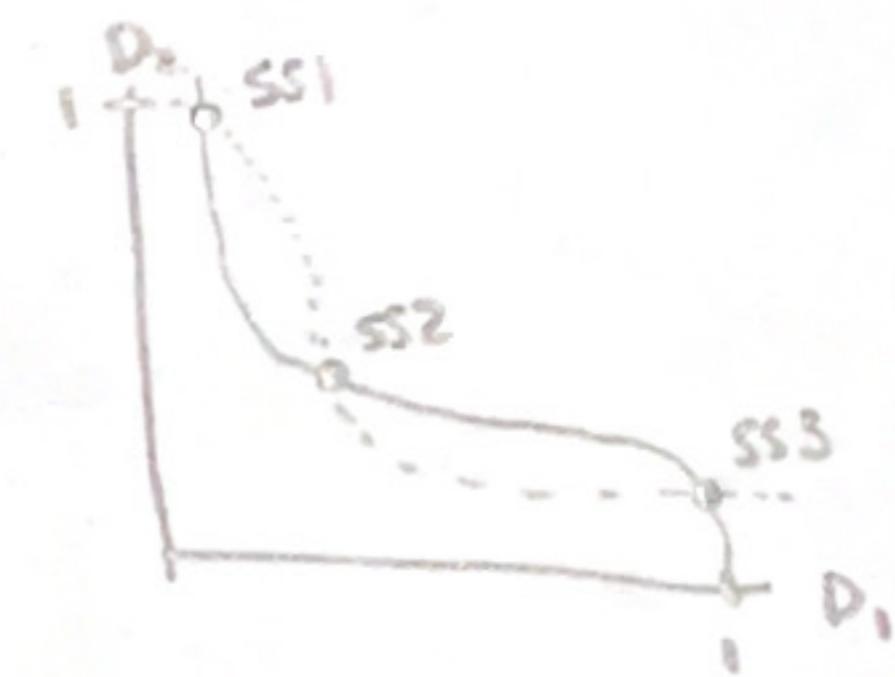
$$\frac{dD_2}{d\tau} = 0 = g(f(D_1) - D_2) \Rightarrow D_2 = g(f(D_1)) = g\left(\frac{D_1^2}{0.1 + D_1^2}\right) = \frac{1}{1 + 10\left(\frac{D_1^2}{0.1 + D_1^2}\right)^2}$$

Run NotchDelta.jl. Phase portrait shows  $\frac{dD_1}{dt}$  in solid line ( $\rightarrow$ ) ,  $\frac{dD_2}{dt}$  in dotted line ( $\cdots$ )

Black lines show different initial states moving to stable SS. Note: trajectories only travel to steady states where high  $D_1$ /low  $D_2$  or low  $D_1$ /high  $D_2$ .

Phase Portrait without trajectories is saved "phase-portrait-nullclines-only.png"

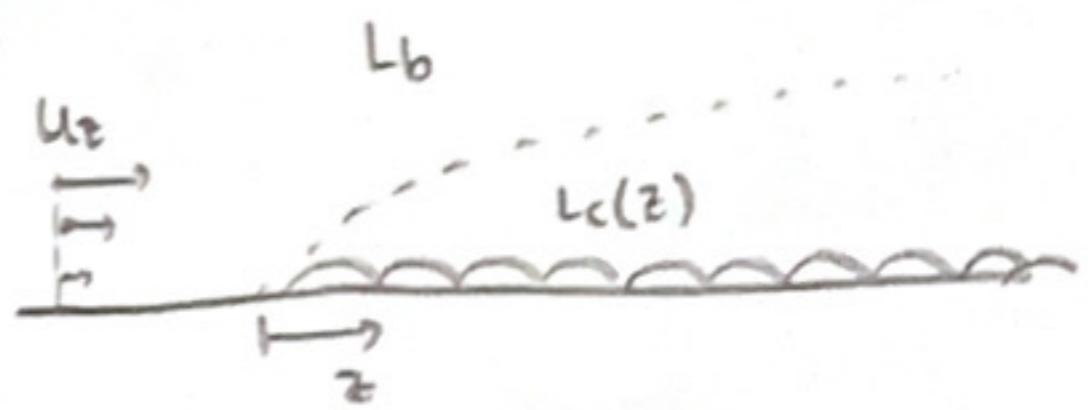
- The cell with high levels of active Delta (cell 2 @ SS1 and cell 1 @ SS3) will assume the primary fate. The opposite cell assumes the secondary fate.



This system is similar to the one studied in class because the two cells differentiate: 1 cell retains the primary fate while the other assumes the secondary fate.

When  $v \ll 1$ ,  $\delta_N \gg \delta_D$ , so I feel like active Notch will quickly be degraded. Because active Notch inhibits the primary fate of the cell, I think its quick degradation in this limit means that it takes a long time for two cells to differentiate when  $v \ll 1$  (compared to the case studied in class).

## 2. Autocrine Signalling + Proliferation : Forced Convection



$$L_c = f(z)$$

$$km = g(z)$$

a)

$$z \frac{dL_c(z)}{dt} = -k_f L_c R_s n_c + k_r R_s^* n_c + km(L_b - L_c) + q n_c$$

$$\text{units: } \frac{\#}{s \cdot m^2} = \frac{m^3}{s \cdot m^2} \cdot \frac{\#}{m^2} \cdot \frac{e}{m^2} + \frac{1}{s} \cdot \frac{\#}{e} \cdot \frac{e}{m^2} + \frac{m}{s} \left( \frac{\#}{m^2 \cdot m^2} \right) + \frac{\#}{s \cdot e} \cdot \frac{e}{m^2} \quad \text{units } \checkmark$$

$$\text{at SS: } \frac{dL_c(z)}{dt} = 0$$

$$0 = -k_f L_c R_s n_c + k_r R_s^* n_c + km(L_b - L_c) + q n_c$$

$$k_f L_c R_s n_c + km L_c = k_r R_s^* n_c + km L_b + q n_c$$

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

$$\frac{\#}{m^3} = \frac{\frac{1}{s} \cdot \frac{\#}{e} \cdot \frac{e}{m^2} + \frac{m}{s} \cdot \frac{\#}{m^2} + \frac{\#}{s \cdot e} \cdot \frac{e}{m^2}}{\frac{m \cdot s \cdot \frac{\#}{e}}{s \cdot s} \cdot \frac{\#}{e} \cdot \frac{e}{m^2} + \frac{m}{s}} = \frac{\frac{\#}{m^2}}{\frac{s}{s \cdot s}} = \frac{\#}{s \cdot m^2} = \frac{\#}{s \cdot m^2 \cdot m^2}$$

units  $\checkmark$

b) if  $K_m \ll 1$  (transport limited)

$$L_c(z) \approx \frac{k_r R_s^* n_c + q n_c}{k_e R_s n_c}$$

The concentration of EFG in the boundary layer is not dependent on  $z$  anymore. The bulk flow does not affect the concentration gradient. The concentration of EFG in the boundary layer region increases due to unbinding from cell surface receptors and synthesis (numerator) and decreases due to binding to receptors (denominator).

if  $K_m \gg 1$  (binding limited)

$$L_c(z) \approx \frac{K_m L_b}{K_m} \approx L_b$$

The concentration of EFG is essentially the bulk concentration and is again no longer  $z$ -dependent. The EFG concentration is essentially the bulk concentration  $L_b$  because EFG diffuses readily from the bulk to the monolayer ( $K_m \gg 1$ ).

c) FROM APRIL 23 LECTURE:

$$\frac{dR_s}{dt} = -k_f L R_s + k_r R_s^* - k_e R_s + V_s \quad (1)$$

$$\frac{dR_s^*}{dt} = k_f L R_s - k_r R_s^* - k_e^* R_s^* \quad (2)$$

$$\frac{dR_i}{dt} = k_e R_s - k_{deg} R_i \quad (3)$$

$$\frac{dR_i^*}{dt} = k_e^* R_s^* - k_{deg} R_i^* \quad (4)$$

at SS, all  $\frac{d}{dt} = 0$

$$R_s^* = \frac{k_f L R_s}{k_r + k_e^*} \quad (5)$$

$$R_i = \frac{k_e R_s}{k_{deg}} \quad (6)$$

$$R_i^* = \frac{k_e^* R_s^*}{k_{deg}} \quad (7)$$

Species balance of  $(R_s + R_s^*)$

$$\frac{d(R_s + R_s^*)}{dt} = -k_e R_s - k_e^* R_s^* + V_s$$

apply SS assumption, solve for  $R_s$

$$R_s = \frac{V_s - k_e^* R_s^*}{k_e} \quad (8)$$

Substitute (8) into (5)

$$R_s^* = \frac{k_f L \left( \frac{V_s - k_e^* R_s^*}{k_e} \right)}{k_r + k_e^*} = \frac{k_f L (V_s - k_e^* R_s^*)}{k_e (k_r + k_e^*)}$$

solve for  $R_s^*$

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

$$R_s^* = \frac{k_f L V_s}{\left( 1 + \frac{k_f L k_e^*}{k_e (k_r + k_e^*)} \right) k_e (k_r + k_e^*)}$$

$$R_s^* = \frac{\frac{k_f \cdot V_s L}{k_e (k_r + k_e^*)}}{1 + \left( \frac{k_e^* k_f L}{k_e (k_r + k_e^*)} \right) \cdot L} = \frac{K_{ss} L}{1 + K_{ss} L} \left( \frac{V_s}{k_e} \right) ; \quad K_{ss} = \frac{k_e^* k_f}{k_e (k_r + k_e^*)} \quad (9)$$

at the limit where  $K_{ss} L \ll 1$ ,

$$R_s^* = K_{ss} L \left( \frac{V_s}{k_e} \right) \quad (10)$$

apply  $L_b = 0$  to answer from a

$$L_c(z) = \frac{k_r k_e^* n_c + q n_c}{k_f R_s n_c + k_m} \quad (11)$$

rearrange (10) for  $L$

$$L_c(z) = \frac{R_s^* k_e^*}{K_{ss} V_s} \quad (12)$$

plug (12) into (5), solve for  $R_s$

$$R_s = \frac{R_s^* (k_r + k_e^*)}{k_f \left( \frac{R_s^* k_e^*}{K_{ss} V_s} \right)} = \frac{(k_r + k_e^*) K_{ss} V_s}{k_f k_e^*} = \frac{K_{ss} V_s}{K_{ss} k_e} = \frac{V_s}{k_e} \quad (13)$$

set (11) = (12)

$$\frac{k_r R_s^* n_c + q n_c}{k_f R_s n_c + k_m} = \frac{R_s^* k_e^*}{K_{ss} V_s}$$

$$K_{ss} V_s (k_r R_s^* n_c + q n_c) = R_s^* k_e^* (k_f R_s n_c + k_m)$$

$$K_{ss} V_s k_r R_s^* n_c - R_s^* k_e^* k_f R_s n_c - R_s^* k_e^* k_m = -K_{ss} V_s q n_c$$

sub (13) in for  $R_s$ , solve for  $R_s^*$

$$R_s^* \left( K_{ss} V_s k_r n_c - k_e^* k_f \frac{V_s}{k_e} n_c - k_e^* k_m \right) = -K_{ss} V_s q n_c$$

$$R_s^* = \frac{-K_{ss} V_s q n_c}{K_{ss} V_s k_r n_c - k_e^* \left( k_f \frac{V_s}{k_e} n_c + k_m \right)} \quad (14)$$

species balance of bound receptor

$$R_T^* = R_i^* + R_s^*$$

sub in (7)

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

sub in (14)

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

$$\frac{1}{c} = \frac{\frac{m}{m^2} \cdot \frac{1}{sc} \cdot \frac{1}{sr} \cdot \frac{E}{m^2}}{\frac{m}{m^2} \cdot \frac{1}{sc} \cdot \frac{1}{sr} - \frac{1}{s} \left( \frac{m^2 m}{s} \frac{E}{sr} \frac{E}{m^2} + \frac{m}{s} \right)} = \frac{\frac{m}{sc}}{\frac{m}{sc} - \frac{1}{s} \left( \frac{m}{s} \right)} = \frac{\frac{m}{sc}}{\frac{m-s}{sc}} = \frac{sc}{m-s} = \frac{1}{c} \quad \text{units } \checkmark$$

$$d) K_{ss} = \frac{k_e^* K_f}{k_e(k_r + k_e^*)} \stackrel{=}{} \frac{\frac{1}{S} \cdot \frac{m^3}{s}}{\frac{1}{S} (\frac{1}{S})} \quad \text{units } \checkmark$$

$$K_{ss} = 8.57 \times 10^{-18} \text{ m}^3$$

$$Sh_z = \frac{km(z)}{\frac{D_L}{z}} = \left( \frac{\frac{1}{S} z^2}{D_L} \right)^{1/3}$$

$$\Rightarrow km(z) = \left( \frac{\frac{1}{S} D_L^2}{z} \right)^{1/3} \stackrel{=}{} \left( \frac{\frac{1}{S} \cdot \frac{m^4}{s^2}}{m} \right)^{1/3} = \left( \frac{m^3}{s^2} \right)^{1/3} = \frac{m}{s} \quad \text{units } \checkmark$$

FROM APRIL 23 LECTURE:

the mitotic rate is proportional to  $R_I^*$

In Excel sheet "2d"  $R_I^*$  vs.  $z$  is plotted on a log-log plot

The  $z$  axis goes from one E.coli cell scale ( $\sim 1 \mu\text{m}$ ) to 10 cm-scale, the size of a lab-scale cell culture container

I'm pretty sure you weren't looking for larger<sup>z</sup> scales than that, but there is also a plot going to 10 m on a standard non-logarithmic plot.

### 3. Enzyme Population in Growing E. coli population

$$\begin{aligned} \dot{m} &= r_{xi} \bar{u}_i - (N + \theta_{mi}) m_i \\ \dot{p} &= r_{li} w_i - (N + \theta_{pi}) p_i \end{aligned} \quad ] \quad \text{at SS, } \dot{m} = 0 \text{ and } \dot{p} = 0$$

$$m_i^* = \frac{r_{xi} \bar{u}_i}{N + \theta_{mi}} \quad p_i^* = \frac{r_{li} w_i}{N + \theta_{pi}}$$

FROM JAN 23 LECTURE:

$$r_{li} = k_{Ei} R_{LT} \left( \frac{m_i}{T_{li} K_{li} + (T_{li} + 1)m_i} \right) \quad (1)$$

FROM PRELIM 1:

$$m_i = K_x \bar{u}_i \quad ; \quad K_x = \frac{r_{xi}}{N + \theta_{mi}} = 0.575 \frac{\text{n mol}}{\text{g DW}}$$

(1) at the limit where  $(1 + T_{li})m_i \ll T_{li}K_{li}$

$$r_{li} = k_{Ei} R_{LT} \left( \frac{m_i}{T_{li} K_{li}} \right)$$

sub into  $p_i^*$

$$p_i^* = \frac{k_{Ei} R_{LT} \left( \frac{m_i}{T_{li} K_{li}} \right)}{N + \theta_{pi}} w_i$$

sub in  $m_i$

$$p_i^* = \frac{k_{Ei} R_{LT} K_x}{T_{li} K_{li} (N + \theta_{pi})} \bar{u}_i w_i$$

$$\Rightarrow \begin{cases} p_i^* = K_L K_x \bar{u}_i w_i \\ K_L = \frac{k_{Ei} R_{LT}}{T_{li} K_{li} (N + \theta_{pi})} \\ K_x = \frac{r_{xi}}{N + \theta_{mi}} = 0.575 \frac{\text{n mol}}{\text{g DW}} \end{cases}$$

$$b) \quad P_i^* = \frac{k_{EI}^L R_{LT} K_x \bar{w}_i w_i}{\tau_{EI} K_{LI} (N + \theta_{PI})}$$

Given:

$$\bar{w}_i = 1$$

$$L_i = 300 \text{ nm}$$

$$K_x = (0.575 \frac{\text{nmol}}{\text{gDW}}) \left( \frac{\text{mmol}}{10^6 \text{nmol}} \right) = 5.75 \times 10^{-7} \frac{\text{mmol}}{\text{gDW}}$$

$$K_{LI} = (200 \frac{\text{nmol}}{\text{L}}) \left( \frac{1 \text{mmol}}{10^3 \text{nmol}} \right) \left( \frac{10^3 \text{L}}{1 \text{m}^3} \right) \left( \frac{1 \text{m}}{10^6 \mu\text{m}} \right)^3 \left( \frac{1 \text{nm}^3}{1 \text{cm}^3} \right) \left( \frac{1 \text{cell}}{1.29 \times 10^{-13} \text{gDW}} \right) = 1.55 \times 10^{-3} \frac{\text{mmol}}{\text{gDW}}$$

calculate  $\theta_{PI}$

$$I = 2e^{-\theta_{PI} t}, \quad t = 24 \text{ hr}$$

$$\frac{1}{2} = e^{-\theta_{PI} \cdot 24}$$

$$\theta_{PI} = \left( -\frac{\ln \frac{1}{2}}{24} \text{ hr}^{-1} \right) \left( \frac{1 \text{ hr}}{3600 \text{ s}} \right) = 8.02 \times 10^{-6} \text{ s}^{-1}$$

calculate  $N$

$$Z = 1 e^{Nt}, \quad t = 40 \text{ min}$$

$$N = \left( \frac{\ln 2}{40} \text{ min}^{-1} \right) \left( \frac{1 \text{ min}}{60 \text{ sec}} \right) = 2.89 \times 10^{-4} \text{ s}^{-1}$$

\* calculate  $k_E^L$

$$k_E^L = \frac{e_L}{\tau_L} \left( \frac{L}{L_i} \right) = \frac{14.5 \frac{\text{aa}}{\text{s}}}{300 \text{ nm}} = 4.83 \times 10^{-2} \frac{1}{\text{s}}$$

find  $k_I$

$$k_I = \frac{1}{\text{translational initiation time}} = \frac{1}{1.5} \text{ s}^{-1}$$

calculate  $\tau_L$

$$\tau_L = \frac{k_E^L}{k_I} = \frac{4.83 \times 10^{-2} \text{ s}^{-1}}{\frac{1}{1.5} \text{ s}^{-1}} = 7.25 \times 10^{-2}$$

calculate  $R_{LT}$

\*\* ribosomes in E. coli cell = 27000  $\frac{\text{ribosomes}}{\text{cell}}$

\*\*\* fraction active ribosomes in E. coli cell = 0.8

$$R_{LT} = (0.8)(27000 \frac{1}{\text{cell}}) \left( \frac{\text{cell}}{1.29 \times 10^{-13} \text{gDW}} \right) \left( \frac{\text{mol}}{6.022 \times 10^{23}} \right) \left( \frac{10^3 \text{mmol}}{1 \text{mol}} \right) = 2.18 \times 10^{-4} \frac{\text{mmol}}{\text{gDW}}$$

### Bionumbers Values

Parameter	value (units)	Bionumbers ref #
* translation elongation rate ( $e_L$ )	14.5 (aa/s)	100233
** ribosomes in E. coli cell	27000 ( $\frac{\text{count}}{\text{cell}}$ )	108946
*** fraction active ribosomes in E. coli cell	0.80	102344

In Excel sheet "3b,c" all parameters are given. I have plotted  $\hat{r}_i$  vs.  $\bar{u}$  in blue.

c) When  $K_p > 1$ , the  $\hat{r}_i^*$  curve becomes steeper (moves up). When more ribosomes can transcribe a single mRNA molecule simultaneously, more protein can be synthesized for a given  $\bar{u}$  value. This is plotted in "3b,c" with  $K_p = 2$  in orange.

## 4. Allosteric Regulation

a) given:

$$F_6P = 0.1 \text{ mM, constant}$$

$$ATP = 2.3 \text{ mM, constant}$$

$$E_i = 0.12 \text{ nM, constant}$$

$$K_{F6P} = 0.11 \text{ mM}$$

$$K_{ATP} = 0.42 \text{ mM}$$

$$k_{cat} = 0.4 \text{ s}^{-1}$$

find kinetic limit

$$r_i = k_{cat} E_i \left( \frac{F_6P}{K_{F6P} + F_6P} \right) \left( \frac{ATP}{K_{ATP} + ATP} \right) = (0.4 \text{ s}^{-1})(0.12 \text{ nM}) \left( \frac{0.1 \text{ mM}}{0.11 \text{ mM} + 0.1 \text{ mM}} \right) \left( \frac{2.3 \text{ mM}}{0.42 \text{ mM} + 2.3 \text{ mM}} \right)$$

$$r_i = (0.019 \frac{\text{nM}}{\text{s}}) \left( \frac{3600 \text{s}}{1 \text{hr}} \right)$$

$$r_i = 69.58 \frac{\text{nM}}{\text{hr}}$$

find  $W_1$  (ATP binds PFK, but AMP doesn't)

$$\text{at } [AMP] = 0, f_1 = 0, \hat{r}_i = 3.003 \frac{\text{nM}}{\text{hr}}$$

from (1)

$$3.003 = 69.58 \frac{W_1}{1 + W_1}$$

$$W_1 = 0.0451$$

find  $W_2$

assume near saturation at  $[AMP] = 0.99 \text{ mM}$ , since  $\hat{r}_i([AMP] = 0.99 \text{ mM}) \approx r_i$

$$f_2 = \frac{\left(\frac{x}{K}\right)^n}{1 + \left(\frac{x}{K}\right)^n}, x \approx 1, \text{ assume } \left(\frac{1}{K}\right)^n > 1$$

$$f_2 \approx 1$$

$$\text{from (1), } [ATP] = 0.99 \text{ mM}$$

$$68.653 = 69.58 \frac{W_1 + W_2 f_2}{1 + W_1 + W_2 f_2}$$

$$W_2 = 74.03$$

$$\hat{r}_i = r_i V_i$$

$$V_i = \frac{W_1 + W_2 f_2}{1 + W_1 + W_2 f_2}$$

$$\hat{r}_i = r_i \frac{W_1 + W_2 f_2}{1 + W_1 + W_2 f_2} \quad (1)$$

$$f_2 = \frac{\left(\frac{x}{K}\right)^n}{1 + \left(\frac{x}{K}\right)^n}$$

b) In Excel "4b,c", I minimized the sum of squared errors for rate.

$$n = 2.490$$

$$K = 0.664$$

c) In Excel "4b,c", it can be seen that the model mostly fits with the measured rate. One point does not fit ( $[AMP] = 0.055\text{mM}$ ).  
I think the model does an okay job describing the data.

In "Extra" I tried to do another iteration of pt a and b. I used the K and n from pt b to recalculate f for calculating  $w_2$ . Using the new  $w_2$ , I calculated new K and n, but the answer actually got worse (the sum of squared errors increases!)