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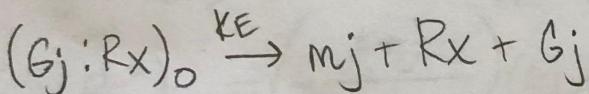
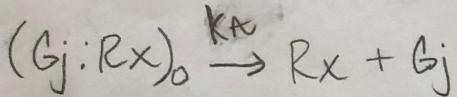
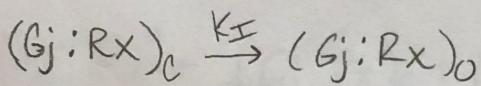
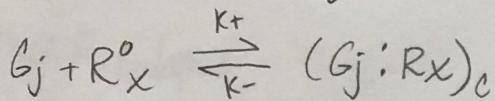
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Prelim 1

Problem 1)

a)

Assume the four elementary steps:



$G_j \rightarrow$  free gene

$R_x^o \rightarrow$  free RNAP concentration

$(G_j : R_x)_o \rightarrow$  open complex

$(G_j : R_x)_c \rightarrow$  closed complex

Kinetic limit of transcription  
↳ elongation rate constant gene j.

$$P_{X,j} = K_{E,j} (G_j : R_x)_o$$

Material balance around open/closed complex

$$\frac{d}{dt}(G_j : Rx)_c = k_{+j}(G_j)(Rx) - k_{-j}(G_j : Rx)_c - k_{Ej}(G_j : Rx)_c$$

$$\frac{d}{dt}(G_j : Rx)_o = k_{Ij}(G_j : Rx)_c - k_{Aj}(G_j : Rx)_o - k_{Ej}(G_j : Rx)_o$$

total RNTP balance

$$Rx_{iT} = Rx^o + (G_j : Rx)_c + (G_j : Rx)_o + \sum_{i=1,j}^N \underbrace{(G_i : Rx)_c + (G_i : Rx)_o}_{k_{xi,j}^{-1}}$$

At steady state,

$$(G_j : Rx^o)_c = \left( \frac{k_{+j}}{k_{-j} + k_{Ej}} \right) (G_j)(Rx)$$

$$(G_j : Rx)_o = \left( \frac{k_{Ij}}{k_{Aj} + k_{Ej}} \right) (G_j : Rx)_c$$

Now we must eliminate closed complex  $(G_j : Rx^o)_c$

$$\text{let, } (G_j : Rx)_o = (k_{xi,j}^{-1})(\tilde{x}_{xi,j}^{-1})(G_j)(Rx^o)$$

Therefore  $Rx_{iT}$  becomes,

$$Rx_{iT} = Rx^o + (k_{xi,j}^{-1})(G_j)(Rx^o) + (k_{xi,j}^{-1})(\tilde{x}_{xi,j}^{-1})(G_j)(Rx^o) + B$$

$$Rx_{iT} = Rx^o + (Kx_{ij}^{-1})(G_j)(Rx^o) + (Kx_{ij}^{-1})(\tilde{x}_{ij}^{-1})(G_j)(Rx^o) + \sum_{i=1,j}^N (Kx_{ii}^{-1})(G_i)(Rx^o) + \sum_{i=1,j}^N (\tilde{x}_{ii}^{-1})(Kx_{ii}^{-1})(G_i)$$

$$Rx_{iT} = Rx^o \left[ 1 + (Kx_{ij}^{-1})(G_j) + (Kx_{ij}^{-1})(\tilde{x}_{ij}^{-1})(G_j) + \sum_{i=1,j}^N (Kx_{ii}^{-1})(G_i) + \sum_{i=1,j}^N (\tilde{x}_{ii}^{-1})(Kx_{ii}^{-1})(G_i) \right]$$

$Rx_{iT}$

$$Rx^o = \frac{1 + (Kx_{ij}^{-1})(G_j) + (Kx_{ij}^{-1})(\tilde{x}_{ij}^{-1})(G_j) + \sum_{i=1,j}^N (Kx_{ii}^{-1})(G_i) + \sum_{i=1,j}^N (\tilde{x}_{ii}^{-1})(Kx_{ii}^{-1})(G_i)}{Rx_{iT}(Kx_{ij})(\tilde{x}_{ij})}$$

$$Rx^o = \frac{(Kx_{ij})(\tilde{x}_{ij}) + (\tilde{x}_{ij})(G_j) + G_j + \sum_{i=1,j}^N \frac{Kx_{ij}\tilde{x}_{ij}G_i}{Kx_{ii}} + \sum_{i=1,j}^N \frac{(Kx_{ij})(\tilde{x}_{ij})}{(\tilde{x}_{ii})(Kx_{ii})}(G_i)}{Rx_{iT}}$$

\* ↓

$$Rx^o = \frac{(Kx_{ij})(\tilde{x}_{ij}) + G_j(1 + \tilde{x}_{ij}) + \sum_{i=1,j}^N \frac{(Kx_{ij})(\tilde{x}_{ij})}{(\tilde{x}_{ii})(Kx_{ii})}(1 + \tilde{x}_{ii})G_i}{\boxed{G_j}}$$

(3)

$$R_{X^0} = \frac{R_{X,IT}(k_{xij})(\tilde{x}_{ij})}{(\tilde{x}_{ij})(k_{xij}) + G_j(1 + \tilde{x}_{ij}) + \varepsilon_j} \quad (4)$$

$$\begin{aligned} R_{xij} &= (k_{Eij})(k_{xij}^{-1})(\tilde{x}_{ij}^{-1})(G_j)(R_{X^0}) \\ &= \frac{(k_{Eij})(k_{xij}^{-1})(\tilde{x}_{ij}^{-1})(G_j) R_{X,IT}(k_{xij})(\tilde{x}_{ij})}{(\tilde{x}_{ij})(k_{xij}) + G_j(1 + \tilde{x}_{ij}) + \varepsilon_j} \end{aligned}$$

$$\boxed{\begin{aligned} R_{xij} &= (k_{Eij})(G_j)(R_{X,IT}) \\ &\quad \frac{(\tilde{x}_{ij})(k_{xij}) + G_j(1 + \tilde{x}_{ij}) + \varepsilon_j}{(\tilde{x}_{ij})(k_{xij}) + G_j(1 + \tilde{x}_{ij}) + \varepsilon_j} \end{aligned}}$$

b) Under what circumstances would an  $N$ -gene system ( $N > 1$ ) be equivalent to the 1-gene system derived in class? (5)

To be equivalent we must force  $E_j$  to zero.

Then only will we recover our desired expression.

So to recover our original derivation of one gene we must consider the relative time scales.

The relative time scales being  $\tau_{X,j}$  vs.  $\tau_{X,i}$ .

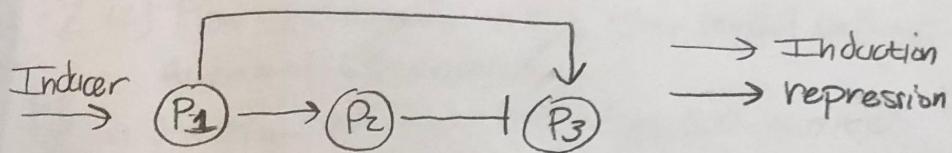
Creating conditions that lead to elongation limitations may achieve what we want but then again we must consider the ratio of time scales.

$$\text{ex. } \tau_{X,j} = \frac{K_{E,j}}{K_{I,j}}, \tau_{X,i} = \frac{K_{E,i}}{K_{I,i}}$$

## Problem 2)

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Analysis of Type 1 in coherent feed forward loop



$$\tau_d = 40 \text{ min} \quad \text{Using tables 1-2.}$$

$$(i) 200 \frac{\text{copies}}{\text{cell}}$$

$$(ii) L_x = 1000 \text{ nt}, L_T = 333 \text{ AA}$$

(iii) Promoter control model Moon/Voigt formulation

(iv) operating at kinetic limit

$$(v) \text{RNAp} = 4600 \frac{\text{copies}}{\text{cell}} ; \text{Ribosome} = 50,000 \frac{\text{copies}}{\text{cell}}$$

$$(vi) L_{x,1} = 1200 \text{ nt}, L_{x,2} = 2400 \text{ nt}, L_{x,3} = 600 \text{ nt}$$

$$\text{let } L_{L,i} = (1/3) L_{x,i}$$

(vii) E. coli weight  $2.8 \times 10^{-13} \text{ g/cell}$  and is 70% water

(viii) half life mRNA 2.1 min

half life protein 24 hrs

$$(ix) \text{RNAp elongation rate } v_x = 60 \frac{\text{nt}}{\text{s}}$$

$$\text{Ribosome elongation rate } v_L = 16.5 \frac{\text{aa}}{\text{s}}$$

$$(x) K_x = 0.24 \frac{\text{nmol}}{\text{g DW}}, K_L = 2.4 \frac{\text{nmol}}{\text{g DW}}$$

a) Simulate response to 10 mM Inducer

(2)

timestep = 1.0 minute

P1 i) run model to steady state without inducer

P2 ii) From steady-state, run the model without inducer for an additional 60 minutes.

P3 iii) Add inducer, run model for 300 minutes

P vs. time