Introduction to Synthetic Biology: Hw3 solution

1. (a)

To express the gene, it's only if the activator binds, and the repressor does not bind. The probability that the activator binds the gene is derived as follows:

$$g + A \underset{k_{1-}}{\overset{k_{1+}}{\rightleftarrows}} g_A$$

$d[g_A]/dt = k_{1+}[g][A] - k_{1-}[g_A] = 0$ (Equilibrium)

→ $k_{1+}[g][A] = k_{1-}[g_A]$

→ $[g] = K_1[g_A]/[A]$ ($K_1 = k_{1-}/k_{1+}$) (1)

The conservation law tells us that

$[g_T] = [g] + [g_A]$ (2)

substitute (1) into (2)

→ $\dfrac{[g_A]}{[g_T]} = \dfrac{[A]}{K_1 + [A]}$

Thus, the probability of A (activator) binds to the gene is

$$P_{A\_bound} = \frac{[A]}{K_1 + [A]} = \frac{[A]/K_1}{1 + [A]/K_1}$$

Similarly, the probability of R (repressor) does not bind to the gene is

$$P_{R\_not\_bound} = 1 - \frac{[R]}{K_2 + [R]} = \frac{1}{1 + [R]/K_2}$$

$$P_{A\_bound\_AND\_R\_not\_bound} = P_{A\_bound} \cdot P_{R\_not\_bound} = \frac{[A]/K_1}{1 + [A]/K_1 + [R]/K_2 + [A][R]/K_1K_2} \quad (3)$$

Therefore, the reaction rate of mRNA is

$$d[m]/dt = \alpha_m \frac{g_{on}}{g_{tot}} - \gamma_m m = \alpha_m (P_{A\_bound} \cdot P_{R\_not\_bound}) - \gamma_m m \quad (4)$$

Substitute (3) to (4), we then obtain the answer

1.(b)

$$g + A \underset{k_{1-}}{\overset{k_{1+}}{\rightleftarrows}} g_A$$

$$g + R \underset{k_{2-}}{\overset{k_{2+}}{\rightleftarrows}} g_R$$

$$d[g_A]/dt = k_{1+}[A][g] - k_{1-}[g_A] \quad (5)$$

$$d[g_R]/dt = k_{2+}[R][g] - k_{2-}[g_R] \quad (6)$$

$$d[g]/dt = -k_{1+}[A][g] - k_{2+}[R][g] + k_{1-}[g_A] + k_{2-}[g_R] \quad (7)$$

In steady state, (5)=(6)=(7)=0

(5)=0 → $[g_A] = [A][g]/K_A$ where $K_A = K_{-1}/K_{+1}$ (8)

(6)=0 → $[g_R] = [R][g]/K_R$ where $K_R = K_{-2}/K_{+2}$ (9)

$$[g_T] = [g_A] + [g_R] + [g] \rightarrow [g_T] = [A][g]/K_A + [R][g]/K_R + [g] \quad (10)$$

$$\frac{[g_{on}]}{[g_T]} = \frac{[g_A]}{[g_T]} = \frac{[A][g]/K_A}{[A][g]/K_A + [R][g]/K_R + [g]} = \frac{[A]/K_A}{[A]/K_A + [R]/K_R + 1}$$

$$\dot{m} = \alpha \frac{[g_{on}]}{[g_T]} + \gamma[m] = \frac{\alpha[A]/K_A}{[A]/K_A + [R]/K_R + 1} + \gamma[m]$$

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(a) equilibrium points: $\dot{P}_1 = \dot{P}_2 = 0$

$$\dot{P}_1 = \frac{\alpha}{1 + P_2/K} - \gamma P_1 = 0 \rightarrow \frac{K\alpha}{K + P_2} = \gamma P_1 \rightarrow K\alpha = \gamma P_1 K + \gamma P_1 P_2 \quad (11)$$

$$\dot{P}_2 = \frac{\alpha}{1 + P_1/K} - \gamma P_2 = 0 \rightarrow K\alpha = \gamma P_2 K + \gamma P_1 P_2$$

(12)

Comparing (11) and (12), $P_1 = P_2$ (13)

Then solving P1 by substituting (13) into (1)

$$\rightarrow P_1 = P_2 = \frac{-\gamma K + \sqrt{\gamma^2 K^2 + 4K\alpha\gamma}}{2\gamma} = \frac{-K + \sqrt{K^2 + 4K\alpha/\gamma}}{2} \quad (14)$$

(For P1 and P2 < 0 is meaningless concentration, so the only equilibrium point is this set.)

The Jacobian at this point is

$$J = \begin{pmatrix} \partial \dot{P}_1/\partial P_1 & \partial \dot{P}_1/\partial P_2 \\ \partial \dot{P}_2/\partial P_1 & \partial \dot{P}_2/\partial P_2 \end{pmatrix} = \begin{pmatrix} -\gamma & \frac{-\alpha}{K(1+P_2/K)^2} \\ \frac{-\alpha}{K(1+P_1/K)^2} & -\gamma \end{pmatrix}$$

Det($J-\lambda I$)=det $\begin{pmatrix} -\gamma-\lambda & \frac{-\alpha}{K(1+P_2/K)^2} \\ \frac{-\alpha}{K(1+P_1/K)^2} & -\gamma-\lambda \end{pmatrix}$

→ $(-\gamma-\lambda)^2 - (\frac{\alpha K}{(K+P)^2})^2 = 0$ ($P = P_1 = P_2$)

→ $\lambda^2 + 2\gamma\lambda + \gamma^2 - (\frac{\alpha K}{(K+P)^2})^2 = 0$

→ $\lambda = \dfrac{-2\gamma \pm \sqrt{4\gamma^2 - 4\left(\gamma^2 - (\frac{\alpha K}{(K+P)^2})^2\right)}}{2}$

→ $\lambda = -\gamma \pm \sqrt{(\frac{\alpha K}{(K+P)^2})^2}$

→ $\lambda = -\gamma \pm \frac{\alpha K}{(K+P)^2}$ (15)

For $\lambda = -\gamma - \frac{\alpha K}{(K+P)^2} < 0$

For $\lambda = -\gamma + \frac{\alpha K}{(K+P)^2}$

→ $\lambda = -\gamma + \dfrac{\alpha K}{(K + \frac{-K+\sqrt{K^2+4K\alpha/\gamma}}{2})^2} = -\gamma + \dfrac{4\alpha K}{(K+\sqrt{K^2+4K\alpha/\gamma})^2}$

If $\dfrac{\alpha K}{(K + \frac{-K+\sqrt{K^2+4K\alpha/\gamma}}{2})^2} < \gamma$, it is stable.

$$\frac{4\alpha K}{(K+\sqrt{K^2+4K\alpha/\gamma})^2}=\frac{4\alpha K}{2K^2+2K\sqrt{K^2+4K\alpha/\gamma}+4K\alpha/\gamma}=\frac{4\alpha}{2K+2\sqrt{K^2+4K\alpha/\gamma}+4\alpha/\gamma}$$

$$=\left(\frac{4\alpha}{2K\gamma+2\sqrt{K^2\gamma^2+4\gamma K\alpha}+4\alpha}\right)\gamma<\gamma$$

The eigenvalues are real and negative, so the equilibrium point is stable.

Since there is only one equilibrium point, the system is not a bistable switch!