1.(a)

$$\frac{d[R^*]}{dt} = k_{on}[R][L] - k_{off}[R^*] \qquad -(1)$$

$$\frac{d[X^*]}{dt} = -\frac{d[X]}{dt} = \frac{V_1[X]}{K_1+[X]} \cancel{+} - \frac{V_2[X^*]}{K_2+[X^*]} \quad -(2), \text{ where } V_1 = \gamma_1[R^*]$$

$$\frac{d[Y^*]}{dt} = \frac{-d[Y]}{dt} = \frac{V_3[Y]}{K_3+[Y]} - \frac{V_4[Y^*]}{K_4+[Y^*]} \qquad V_3 = \gamma_3[X^*] \quad -(3)$$

$$R_T = [R]+[R^*] \qquad -(4)$$

$$X_T = [X]+[X^*] \qquad -(5)$$

$$Y_T = [Y]+[Y^*] \qquad -(6)$$

$$k_{on}[R][L] = k_{off}[R^*]$$

$$\Rightarrow k_{on}([R_T]-[R^*])[L] = k_{off}[R^*]$$

$$\Rightarrow \frac{1}{\theta_B} - 1 = K_D \Rightarrow \boxed{\theta_B = \frac{1}{K_D+1}} \quad \text{where } \theta_B = \frac{[R]}{[R_T]}, \; K_D = \frac{k_{off}}{k_{on}[L]}$$

@ SS (2)

$$\frac{V_1[X]}{K_1+[X]} = \frac{V_2[X^*]}{K_2+[X^*]} \Rightarrow \frac{V_1}{V_2} = \left(\frac{\gamma_1\theta_B}{V_2}\right)R_T = \frac{[X^*]}{[X]} \cdot \frac{K_1+[X]}{K_2+[X^*]}$$

$$\Rightarrow \frac{V_1([X_T]-[X^*])}{K_1+([X_T]-[X^*])} = \frac{V_2[X^*]}{K_2+[X^*]}$$

$$\Rightarrow \frac{V_1}{V_2}\left[\frac{1}{x^*}-1\right] = \frac{K_1+([X_T]-[X^*])}{K_2+[X^*]}$$

$$\Rightarrow \frac{V_1}{V_2}\frac{(1-x^*)}{x^*} = \cancel{\frac{K_1+x^*}{K_2+}} \; \frac{K_1+(1-x^*)}{K_2+x^*}$$

$$\Rightarrow \boxed{\frac{V_1}{V_2} = \frac{K_1+(1-x^*)}{K_2+x^*}\left(\frac{x^*}{1-x^*}\right)} \quad -A$$

$$\|^{ly} \quad \frac{V_3}{V_4} = \frac{K_3+(1-y^*)}{K_2+\cancel{y^*}}\left(\frac{y^*}{1-y^*}\right)$$

$$\frac{V_3}{V_4} = \left(\frac{\gamma_3 x^*}{V_4}\right) X_T = 10x^* \quad \frac{V_1}{V_2} = \left(\frac{\gamma_1 \theta_B}{V_2}\right) R^T = \cancel{10R^T}\ 5\theta_B$$

$$\therefore \quad \boxed{5\theta_B = \frac{k_1 + (1-x^*)}{k_4 + x^*}\left(\frac{x^*}{1-x^*}\right)}$$

$$\boxed{10x^* = \frac{k_3 + (1-y^*)}{k_4 + y^*}\left(\frac{y^*}{1-x^*}\right)}$$

$$\Rightarrow \boxed{y^* = \frac{-e \pm \sqrt{e^2 - 4df}}{2d}} \quad \text{where} \quad \begin{aligned} d &= (1-10x^*) \\ e &= -(1+k_3) + (1-k_4) \times 10x^* \\ f &= 10x^* k \end{aligned}$$

$$\boxed{x^* = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}} \quad \text{where} \quad \begin{aligned} a &= 1 - 5\theta_B \\ b &= -(1+k_4) + (1-k_2) \times 5\theta_B \\ c &= 5\theta_B k; \end{aligned}$$

Substituting x^* in y^* eq^n we can get y^* in terms of input.

1(d). Percentage changes from plots:

$k = 0.1$

$$\text{Change in } \theta_B = \frac{0.1304 - 0.09093}{0.09093} = \frac{\text{Value at } 0.15 - \text{value at } 0.1}{\text{Value at i/p } 0.1} \times 100 = 43.407\%.$$

$$\text{Change in } x^* = \cancel{\frac{0.3897 - 0.3046}{0.3}} \quad \frac{0.8263 - 0.1646}{0.1646} \times 100 = 402.005\%.$$

$$\text{Change in } y^* = \frac{0.1406 - 0.06963}{0.06963} \times 100 = 130.7566\%$$

$k = 10.$

$$\text{Change in } \theta_B = \frac{0.1304 - 0.09093}{0.09093} \times 100 = 43.407\%$$

Change in $x^* = \dfrac{0.3897 - 0.3046}{0.3046} \times 100 = 27.9383\%$.

Change in $y^* = \dfrac{0.8051 - 0.762}{0.762} \times 100 = 5.6562\%$.

1, 1, 1

1(c) Hill coefficients (Using MATLAB curve fitting tool)

For $k = 10$

$$o/p = \frac{A \times (i/p)^n}{(i/p)^n + C^n}$$

θ vs $\frac{1}{K_d}$, $A = 1, C = 1, n = 1$

x^* vs $\frac{1}{K_d}$, $A = 0.8566$, $C = 0.1804$, $n = 1.013$

y^* vs $\frac{1}{K_d}$, $A = 0.9099$, $C = 0.02038$, $n = 1.029$

For $k = 0.1$

θ vs $\frac{1}{K_d}$, $A = 1$, $C = 1$, $n = 1$

x^* vs $\frac{1}{K_d}$ $A = 0.9867$, $C = 0.2501$, $n = 3.208$

y^* vs $\frac{1}{K_d}$, $A = 0.9929$, $C = 0.1239$, $n = 6.982$

1.e

2.(a) S.S. when no inhibitor, $[I_1]=[I_2]=0$,

$V_{max1} = V_{max2} = 5$, $V_{max3} = V_{max4} = 1$, $K_{S1} = K_{S2} = K_{S3} = K_{S4} = 5$, $K_{I1} = K_{I2} = 1$

From (1) $$V_1 = \frac{5[A]}{5+[A]}$$

From (2) $$V_2 = \frac{5[A]}{5+[A]}$$

From (3) $$V_3 = \frac{\cancel{5}[B]}{5+[B]}$$

From (4) $$V_5 = \frac{\cancel{5}[C]}{5+[C]}$$

From (5) @ S.S, $V_1 = V_3 \Rightarrow \frac{5[A]}{5+[A]} = \frac{\cancel{5}[B]}{5+[B]}$ — (A)

$V_2 = V_4 \Rightarrow \frac{5[A]}{5+[A]} = \frac{\cancel{5}[C]}{5+[C]}$ — (B)

From (A) & (B), $\boxed{[B]=[C]}$

Now, $100 = [A]+[B]+[C]$

$\Rightarrow 100 = [A] - 2[B] \Rightarrow [A] = 100-2[B]$

From (A)

$$\frac{5(100-2B)}{5+(100-2B)} = \frac{B}{5+B}$$

$\Rightarrow 8B^2 - 345B - 2500 = 0$

$\Rightarrow B = -6.32$, $\underline{B = 49.445}$

↳ This is in line with constraints

$\therefore$ $[B] = [C] = 49.445$ units

$[A] = 100 - 2 \times 49.445 = 1.11$ units @ S.S

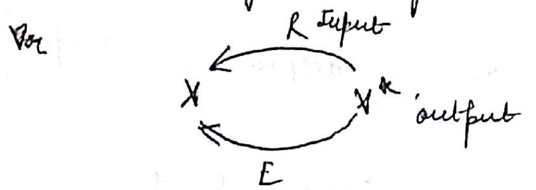
1.(e) The amplification of a signal depends on input parameters and zero-order ultrasensitivity:

$\cancel{\frac{11a}{5+a} = 100}$

$\Rightarrow \cancel{500 + 100a = 11a}$

a^2

If we have a system of this type:



where V_R = velocity of receptor interaction reaction

V_E = velocity of backward rxn

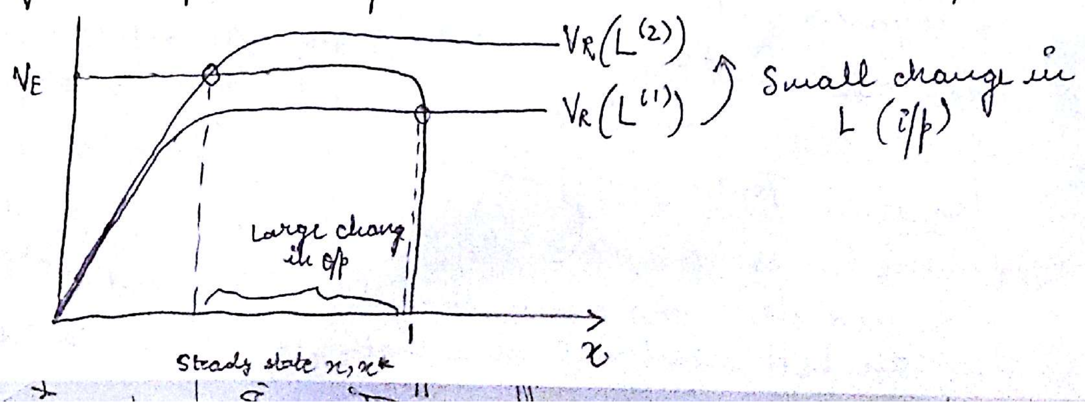
and V_R is a fn. of ligand concn $[L]$

For e.g: $V_{R,t} = \frac{V_{R\,max}[L]}{K_D + [L]}$

then a large change in output / amplification of input signal is observed when the following condns are satisfied:

1. System is a zero order ultrasensitive system, i.e $K \ll 1$
2. System operates near saturation, $V_E \approx V_R(L)$

These parameters need to be highly tuned in order to recieve a large change in response due to small change in output



If these cond's are not met then a small change in L will not lead to a large change in o/p and hence no amplification will take place.

As seen in 1b, for $k=0.1$, the graph has ~~a sigmoi~~ obeys zero order ultrasensitivity. A small change in i/p (0.1 to 0.15) leads to a 402.005% increase in x^* and 130.7566% increase in y^*.

When the same circuit is operated at $k=10$, there is a very small change in y^* (5.65%) and x^* (27.9383%) for same change in i/p

Just changing the value k can help adjust the amplification response of the circuit.

2.(b) It resembles an AND gate to some extent.

2.(C) The given circuit is an AND gate. The steady state levels of A are low at low inhibitor conc's and high at high inhibitor concⁿ. But if we look at the graph, even when one of the concentrations is 0, the concⁿ of A is less. So, it's an AND gate if we consider higher concⁿ of inhibitor to be 1 and lower concⁿ to be zero.
Though from the graph there isn't a clear zero visible, this can lead to the operator being fuzzy.

2.(d)

As described in Goldbeter and ~~Koshland~~, if we measure the response coefficient, an ~~small~~ 81-fold change in ligand is required to achieve activity change from 10% to 90% change in maximal activity. However, for a system operating in the 0-order ultrasensitive region by a 3-fold or lower change in ligand. This is seen when Hill coefficient ≈ 4, but such high Hill coefficients are rare among cooperative proteins. So this type of covalent modification offers a "tight" control of a biological system. This type of sensitivity is important because in certain futile cycles, where one system needs to be turned on and the other turned off, zero-order sensitivity is needed. A steady state can be achieved in a matter of milliseconds.