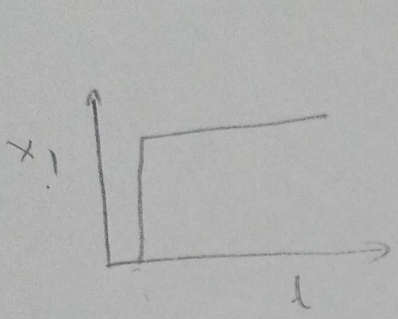
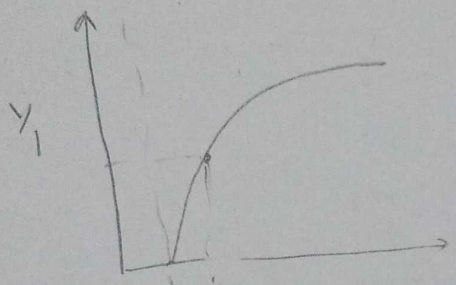
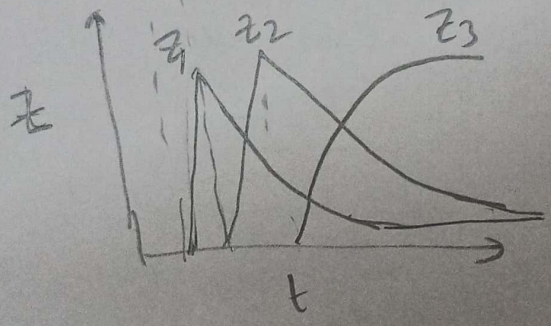
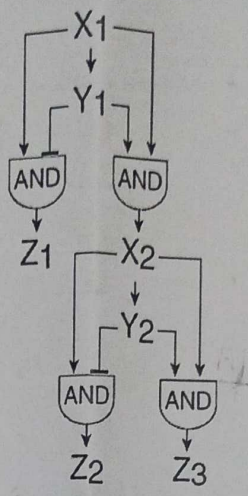
1. Draw the profile of Z1, Z2 and Z3. **[2 marks]**



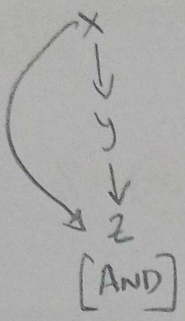


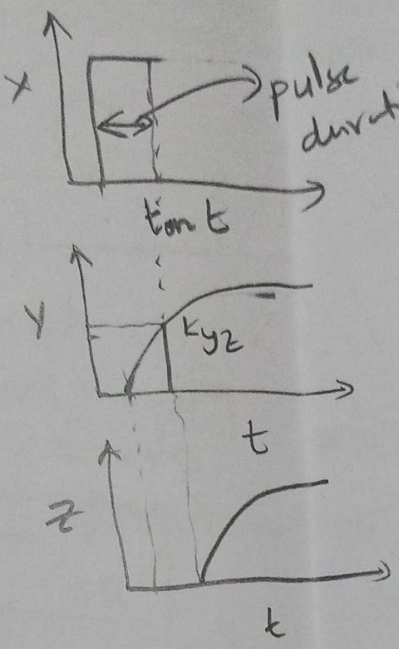




2. Design a gene circuit to filter out short, noisy inputs while responding to a sustained signal. What is the minimum pulse duration of signal is required to activate the response? **[2 marks]**

gene circuit C-FFL





$$Y = Y_{st}\left(1 - e^{-\alpha_y \cdot t}\right)$$

$$K_{yz} = Y_{st}\left(1 - e^{-\alpha_y t_{on}}\right)$$

$$t_{on} = \frac{1}{\alpha_y} \ln\left(\frac{1}{1 - \frac{K_{yz}}{Y_{st}}}\right)$$

other options

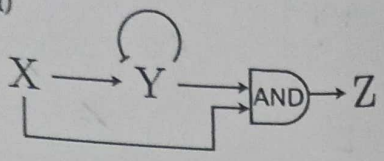
$X \rightarrow Y \rightarrow Z$

$X \rightarrow Y \rightarrow Z$

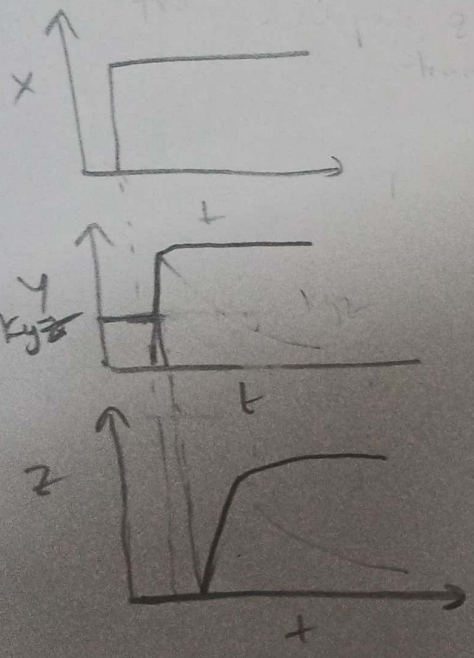
3. (a) The regulator Y in FFLs in transcription networks is often negatively autoregulated. How does this affect the dynamics of the circuit, assuming that it has an AND input function at the Z promoter? (b) The *Y* regulator in an OR gate FFL is often positively autoregulated. How does this affect the dynamics of the circuit?

[3 marks]

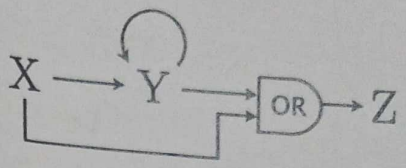
a)



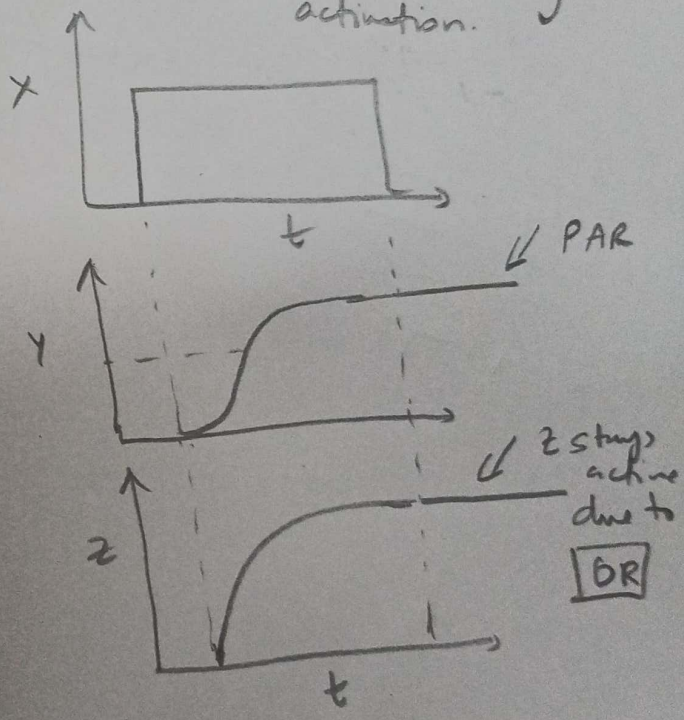
NAR helps to speed up the reponse time. So Y can accumulate faster. Y will reach the "kyz" threshold quickly, thereby speeding up Z accumulation.



b)

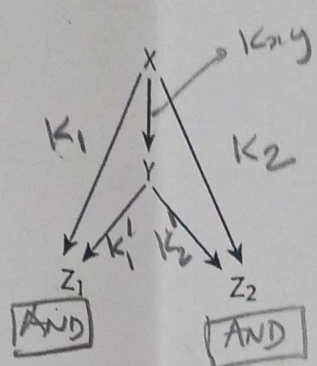


PAR delay Y accumulation. Y can stay it self active in absence of X post its activation. Z accumulates immediately with X activation.

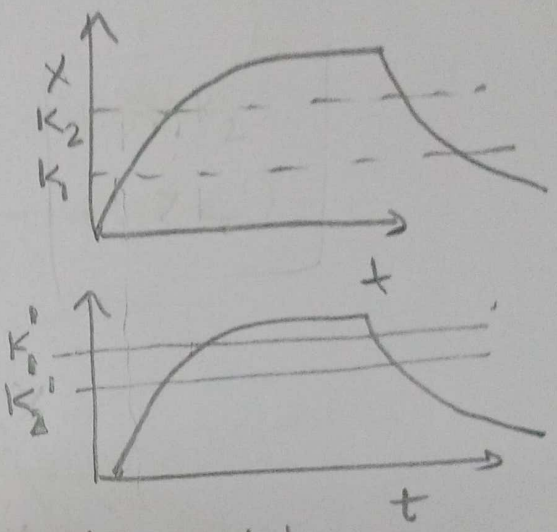


4. What is the temporal order of turn ON and turn OFF in a multi-output coherent feedforward where all genes are regulated by AND gates? Which thresholds determine the ON and OFF orders of Z_1 and Z_2? Can one obtain FIFO (first in and first out) orders? For example, Z_1 appears and disappears first with increase and decrease in X, respectively. **[3 marks]**

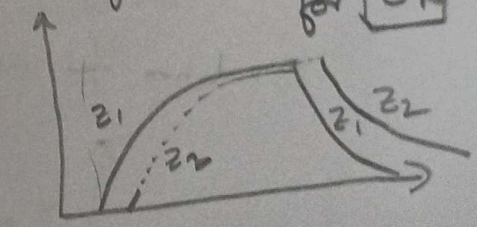
K_1, K_2, K_1', K_2' determine the order of activation of Z_1 and Z_2



We cannot obtain FIFO with AND but only with "OR"

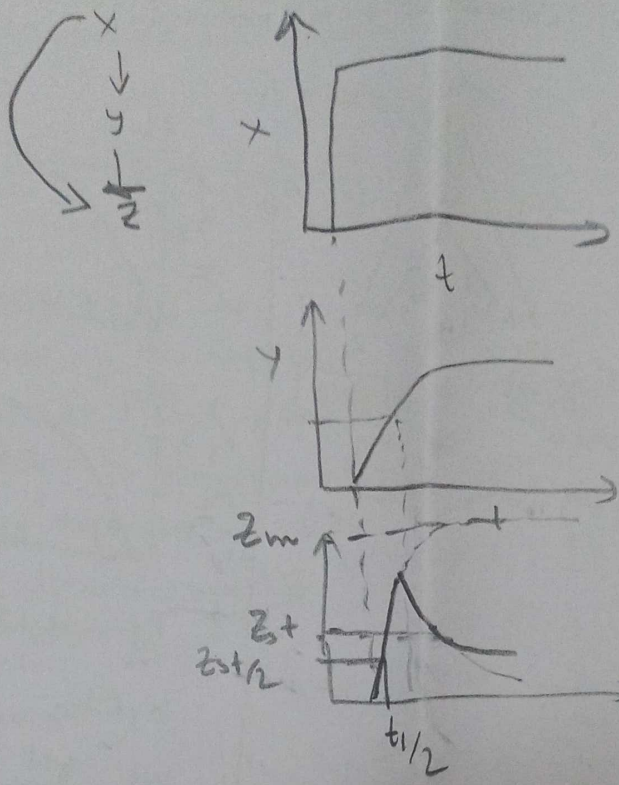


If we take, $K_1 < K_2$, $K_1' > K_2'$ we get FIFO, but only for OR



Z_1 comes first and goes out first

5. Calculate the response time for incoherent feed forward loop and compare it with simple regulation. What is the condition for adaptation? [3 marks]



$$Z = Z_m\left(1 - e^{-\alpha_z t}\right)$$

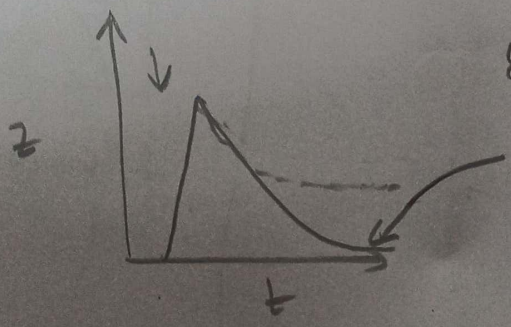
$$\frac{Z_{st}}{2} = Z_m\left(1 - e^{-\alpha_z \cdot t_{1/2}}\right)$$

$$\frac{1}{2} = F\left(1 - e^{-\alpha_z \cdot t_{1/2}}\right)$$

$$e^{-\alpha_z \cdot t_{1/2}} = 1 - \frac{1}{2F}$$

$$t_{1/2} = \frac{1}{\alpha_z} \ln\left(\frac{2F}{2F-1}\right)$$

Condition for adaptation is



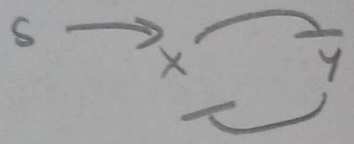
It should come back to pre-stimulus level

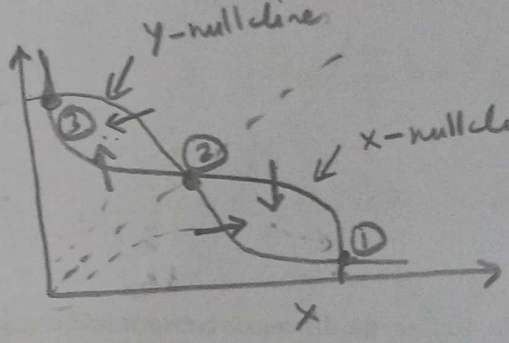
6. Define nullclines. Use nullclines to show that mutual inhibition between X and Y proteins can give rise to bistable characteristics. Write the relevant equations. Show how trajectories cross nullclines? If signal S activates X independently, sketch how the steady state of X changes with S. **[5 marks]**

$\frac{dx}{dt} = f(x,y)$ $\frac{dy}{dt} = g(x,y)$

$\frac{dx}{dt} = 0$ x_{ss} vs y (x-nullclines)

$\frac{dy}{dt} = 0$ y_{ss} vs x (y-nullclines)





$\frac{dx}{dt} = \beta_x \frac{k_x^n}{k_x^n + y^n} - \alpha_x \cdot x$

$\frac{dy}{dt} = \beta_y \cdot \frac{k_y^n}{k_y^n + x^n} - \alpha_y \cdot y$

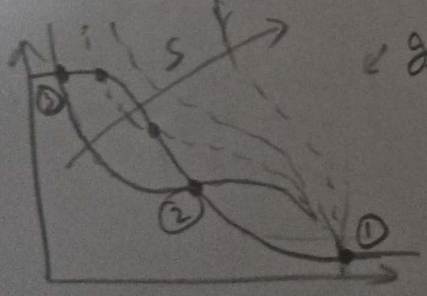
① & ③ stable
② unstable

$n >> n$ ⇒ to get bistable

If S activates X independently

$\frac{dx}{dt} = \beta_x' \cdot S + \beta_x \cdot \frac{k_x^n}{k_x^n + y^n} - \alpha_x \cdot x$

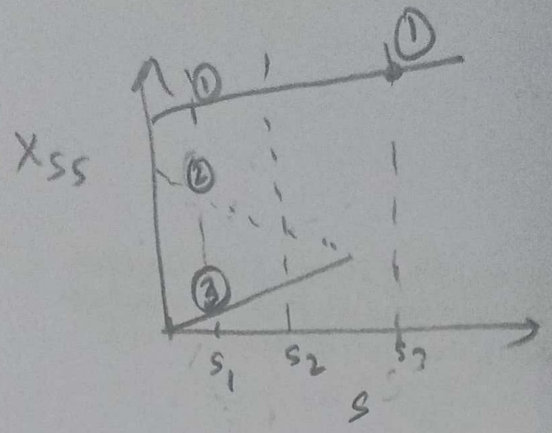
With change in S, number of intersection of x and y nullclines is going to change.



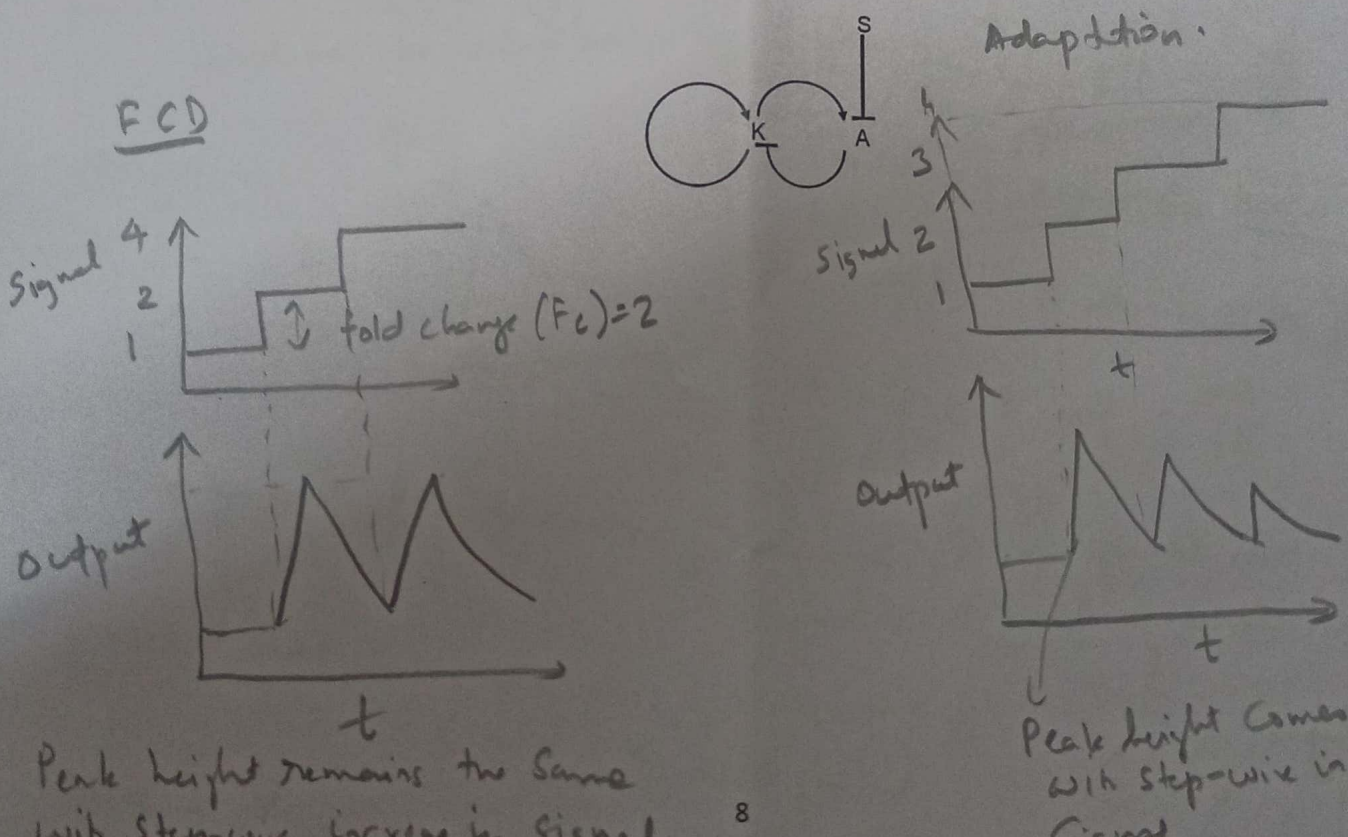
If S becomes large, only one steady state remains ① ⇒ high X, low Y

Now we can show X_{ss} vs S plot

(PTO)

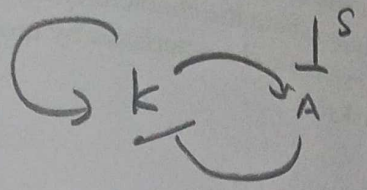


7. Explain the difference between fold change detection (FCD) and adaptation? What is the relationship between these two characteristics. Show that the given circuit exhibit FCD. **[5 marks]**



Relationship

Any network that shows FCD will also show adapation. On the other hand, vice versa is not true (Adapatation network need not show FCD)



$$\frac{dA}{dt} = \beta_A \cdot \left(\frac{k}{s}\right) - \alpha_A \cdot A$$

$$\frac{dk}{dt} = \beta_k \cdot k - \alpha_k \cdot k$$

Condition for FCD

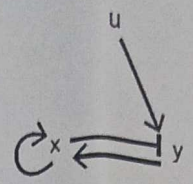
$$\frac{dA}{dt} = g(\lambda s, \lambda k, A) = g(s, k, A)$$

$$\Rightarrow \frac{dA}{dt} = \beta_A \left(\frac{\lambda k}{\lambda s}\right) - \alpha_A \cdot A = \beta_A \left(\frac{k}{s}\right) - \alpha_A \cdot A$$

$$\frac{dk}{dt} = f(\lambda s, \lambda k, A) = \lambda f(s, k, A)$$

$$\Rightarrow \frac{dk}{dt} = \beta_k \cdot \lambda k - \alpha_k \cdot \lambda k = \lambda \left(\beta_k \cdot k - \alpha_k \cdot k\right)$$

8. Write the equation for the given system. Demonstrate that the system can exhibit oscillatory characteristics by drawing the phase plane. Comment about the characteristics of the oscillations. Discuss how the system can exhibit excitable characteristics by modifying the parameters or structure of the phase plane. **[5 marks]**

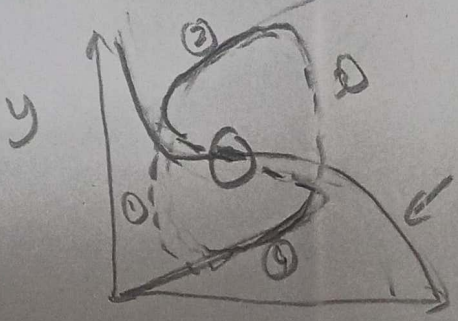


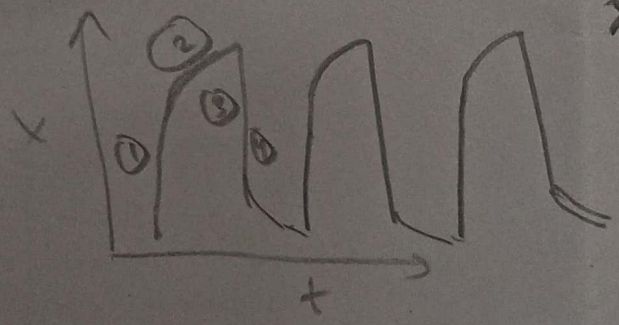
$$\frac{dx}{dt} = \beta_x \left(\frac{x^h}{x^h + k^h}\right)\left(\frac{y^h}{y^h + k^h}\right) - \alpha_x \cdot x$$

$$\frac{dy}{dt} = \beta_y \cdot \left(\frac{k_y^h}{k_y^h + x^h}\right) u - \alpha_y \cdot y$$

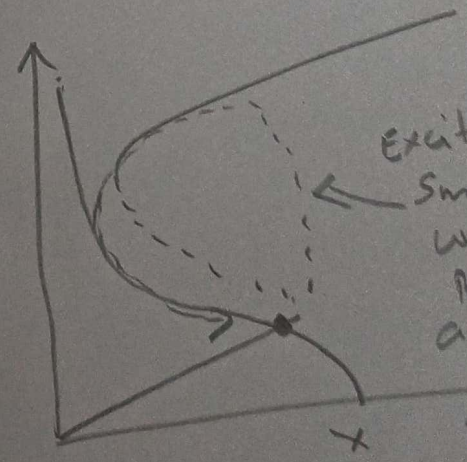
x-nullcline.

X-nullcline will be Bistable





Saw-toothed shapped



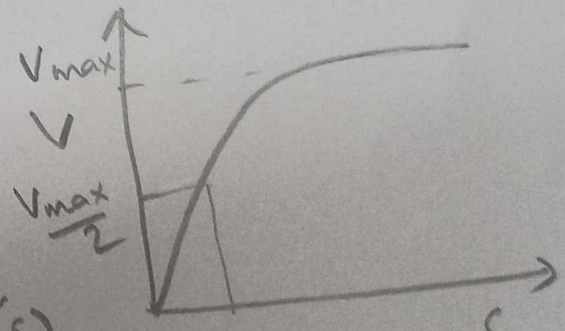
Excitable System. Small perturbation will go around Bistable switch and comes back to stable steady state.

9. A biochemical reaction involves binding of a substrate (S) to enzyme (E) forming modified substrate (Sp). **[5 marks]**

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + Sp$$

Write the rate expression for the formation of the modified substrate (Sp). Explain the role of different parameters in the reaction. Illustrate how varying these parameters affects the rate using appropriate plots.

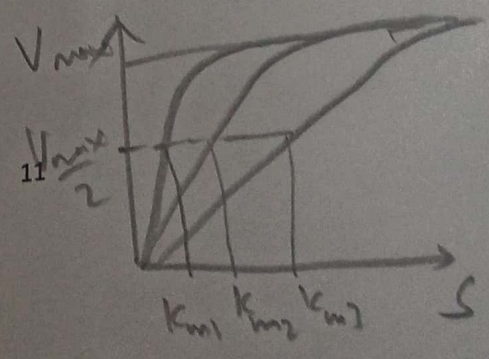
$$V = \frac{V_{max} \cdot S}{K_m + S}$$



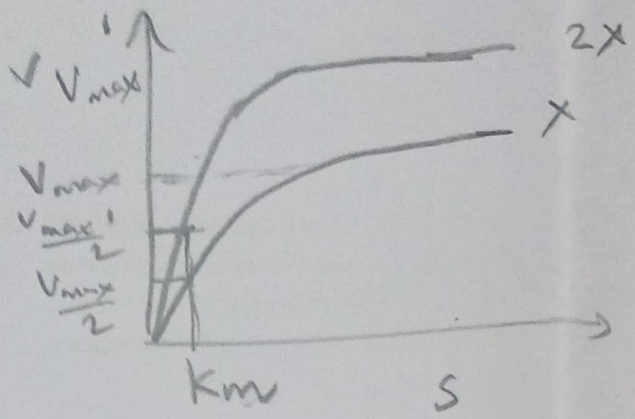
K_m is like affinity Constant
Small K_m means that Substrate (S) Conc required is very small to reach V_{max}. It is a better Substrate Compared to another Substrate with high K_m value

$$V_{max} = k_2 \cdot E$$

$$K_m = \frac{k_{-1} + k_2}{k_1}$$



PTO



Enzyme concentration is increased 2 fold
Vmax increase
but Km is Unchanged

10. Describe how a protein modification, such as phosphorylation by a kinase and dephosphorylation by a phosphatase, contributes to signal propagation within a cell. **[2 marks]**

Protein modification and demodification steps are used for propagation