

Textbooks X

Prof: Spandan

Modern Control Engineering - Ogata

H2: Prof: Vinod PK

Systems

Thinking

Systems Thinking

System Modelling

Frequency Analysis

Time Analysis

→ Laplace Transform :-

$$\circ v(t) \longrightarrow \frac{1}{s}$$

$$\circ tv(t) \longrightarrow \frac{1}{s^2}$$

$$\circ t^n v(t) \longrightarrow \frac{n!}{s^{n+1}}$$

$$\circ e^{at} v(t) \longrightarrow \frac{1}{s-a}$$

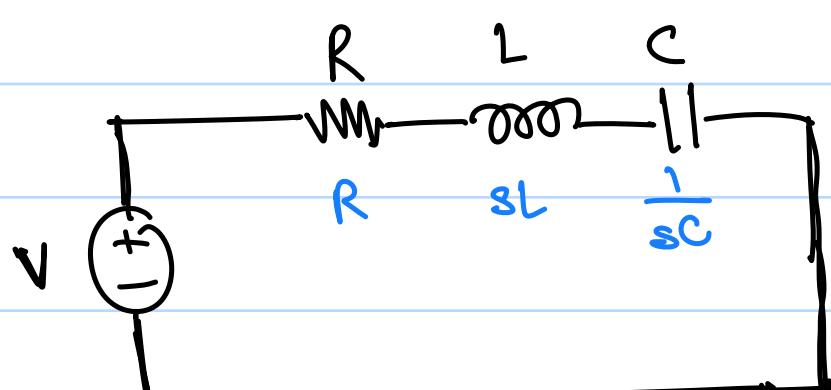
$$\circ \sin(at) \longrightarrow \frac{a}{s^2 + a^2}$$

$$\circ \cos(at) \longrightarrow \frac{s^2}{s^2 + a^2}$$

Check Again

° Applying Laplace in RLC :-

$$Z = R + sL + \frac{1}{sC}$$



$$Z = \frac{sRC + s^2 LC + 1}{sC}$$

$$I(s) = \frac{V(s)}{Z} = \frac{VsC}{sRC + s^2 LC + 1} = Vs \left(\frac{1}{sR + s^2 L + \frac{1}{C}} \right)$$

$$V_R = iR$$

\Rightarrow

$$V = iR + \frac{1}{C} \int i dt + L \frac{di}{dt}$$

$$V_C = \frac{1}{C} \int i dt$$

$$\Rightarrow V = \frac{di}{dt} R + \frac{i}{C} + L \frac{d^2 i}{dt^2}$$

$$V_L = L \frac{di}{dt}$$

$$= V(t) = \frac{1}{C} i + \frac{di}{dt} R + \frac{d^2 i}{dt^2} L$$

$$\Rightarrow V(s) = \frac{I}{C} + sRI + s^2 LI$$

$$\Rightarrow V(s) = I \left(s^2 L + sR + \frac{1}{C} \right)$$

$$s^2 L + sR + \frac{1}{C} = 0 \Rightarrow s = \frac{-R \pm \sqrt{R^2 - 4LC}}{2L}$$

$$\Rightarrow s_1 = \frac{-R - \sqrt{R^2 - 4LC}}{2L}$$

$$s_2 = \frac{-R + \sqrt{R^2 - 4LC}}{2L}$$

$$V(s) = I(s)(s - s_1)(s - s_2)$$

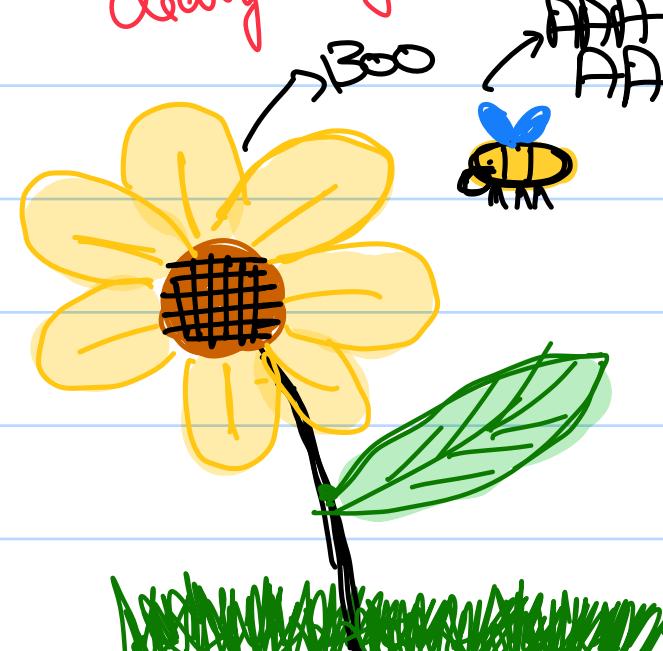
Personal Note:

Write everything
clearly again

$$I(s) = \frac{V(s)}{(s - s_1)(s - s_2)}$$

$$H(s) = \frac{1}{(s - s_1)(s - s_2)}$$

① ②



$$\textcircled{1} \rightarrow \frac{1}{s-s_1} \xrightarrow{t} e^{s_1 t} v(t)$$

$$\frac{1}{s-s_2} \xrightarrow{t} e^{s_2 t} v(t)$$

$$\begin{aligned} \Rightarrow h(t) &= \int_{-\infty}^{\infty} e^{s_1 \tau} v(\tau) e^{s_2 t - \tau} v(t - \tau) d\tau \\ &= e^{s_2 t} \int_0^{\infty} e^{s_1 \tau - s_2 \tau} \cancel{v(\tau)} v(t - \tau) d\tau \\ &= e^{s_2 t} \int_0^t e^{(s_1 - s_2) \tau} d\tau \end{aligned}$$

$$\begin{aligned} \Rightarrow h(t) &= e^{s_2 t} \left[\frac{1}{(s_1 - s_2)} e^{(s_1 - s_2) t} \right]_0^t \\ &= \frac{e^{s_2 t}}{s_1 - s_2} (e^{(s_1 - s_2) t} - 1) \end{aligned}$$

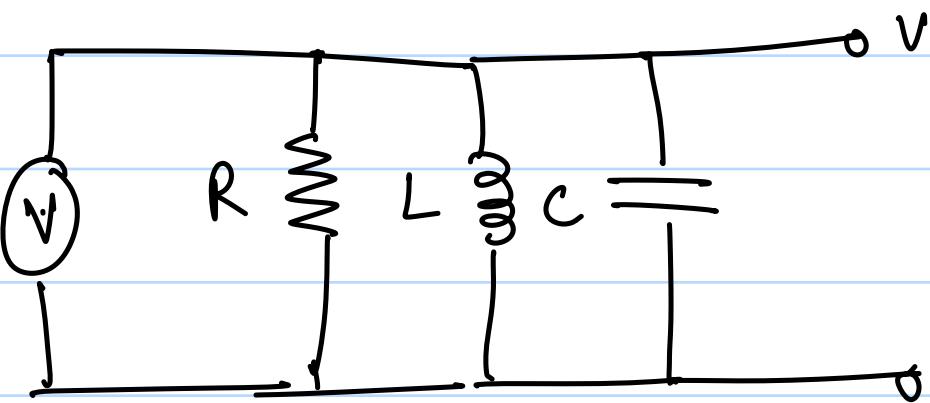
$$i(t) = v(t) * h(t)$$

$$= V \int \frac{e^{s_2 t}}{(s_1 - s_2)} (e^{(s_1 - s_2) t} - 1) dt$$

$$= V \int \frac{e^{s_1 t}}{s_1 - s_2} - \frac{e^{s_2 t}}{s_1 - s_2} dt$$

$$\text{What?} = \frac{V}{s_1 - s_2} \int_{-\infty}^{\sim} e^{s_1 t} - e^{s_2 t} dt$$

$$= \frac{V}{s_1 - s_2} \left[\left(\frac{1}{s_1} \right) [e^{s_1 t}]_{-\infty}^{\infty} - \left(\frac{1}{s_2} \right) [e^{s_2 t}]_{-\infty}^{\infty} \right]$$



Voice
Review

System
Thinking

Awesome

This is boring

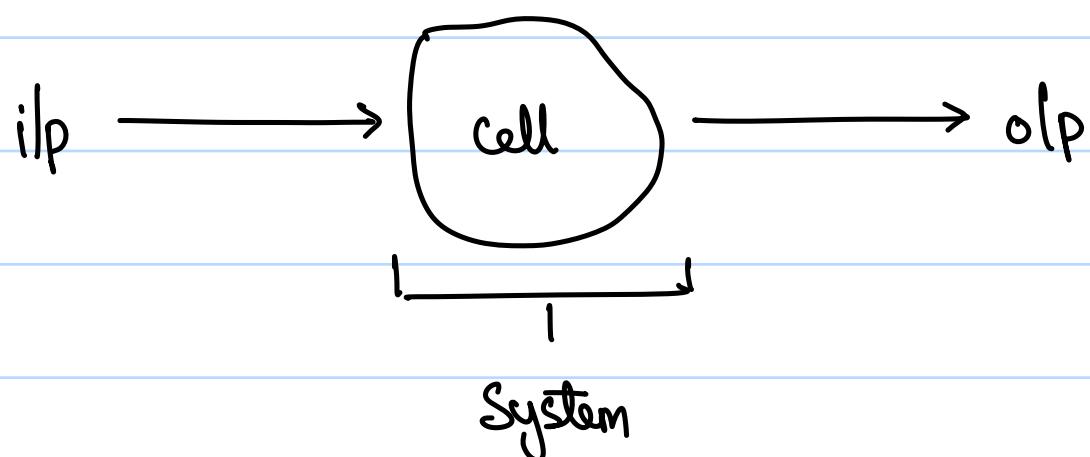
Systems Thinking - H2

→ Summary of H1 :-

- Block Diagrams, transfer functions
- Modelling of a system using the governing equation (first principles) in the form of ODE's. (Time Domain)
- Laplace Transform and s Domain Analysis for the ODE's, in the form of algebraic analysis.
- 1st order systems and 2nd order systems.
- Feedback Controllers (P, PI, PD, PID)
- Steady state Error and Stability.

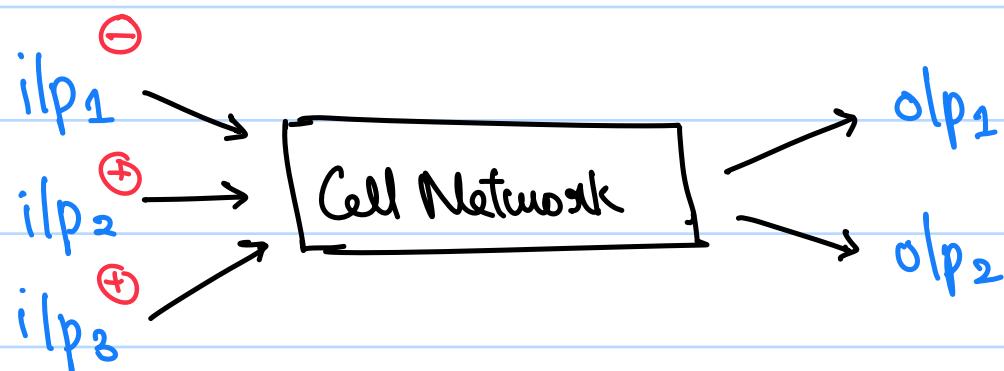
→ Biological Systems :-

- Spans the time and length scales.



- The response of a cell includes growth, death, movement, division, secretion and differentiation (change into a different cell)

- Most biological systems are MIMO (Multi-Input Multi-Output) systems.

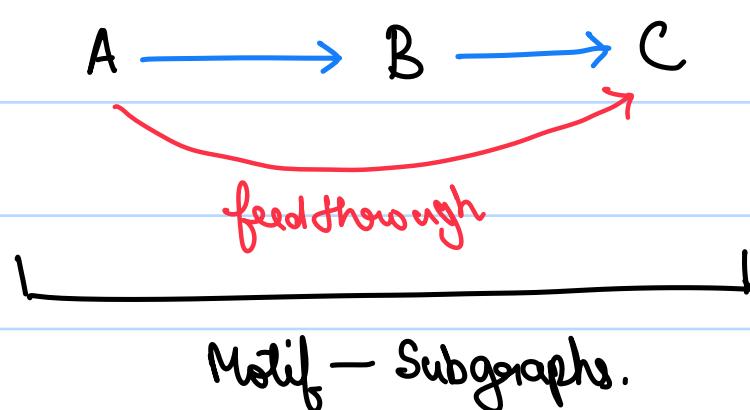


- ilps and olps of a biological system are discrete, but the behavior of the system can be modelled using continuous-time ODEs.

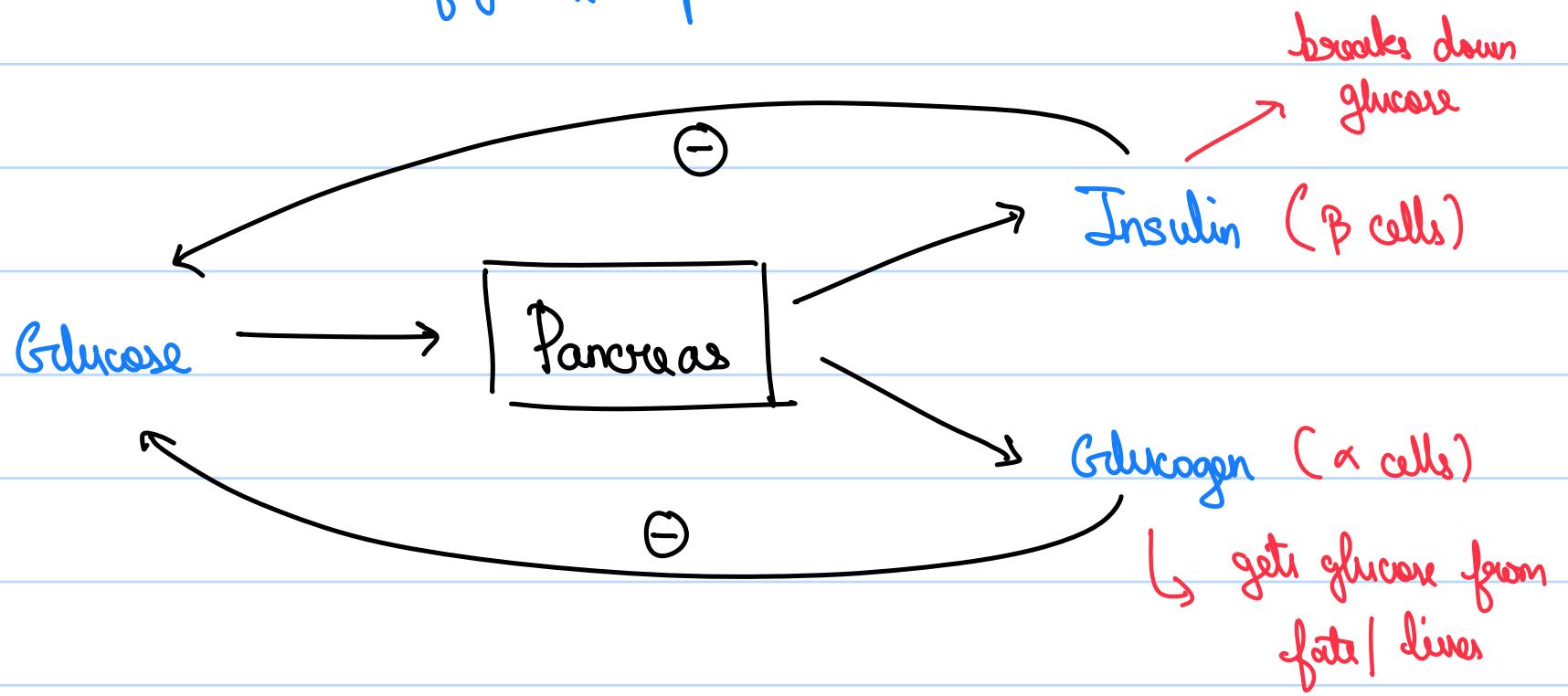
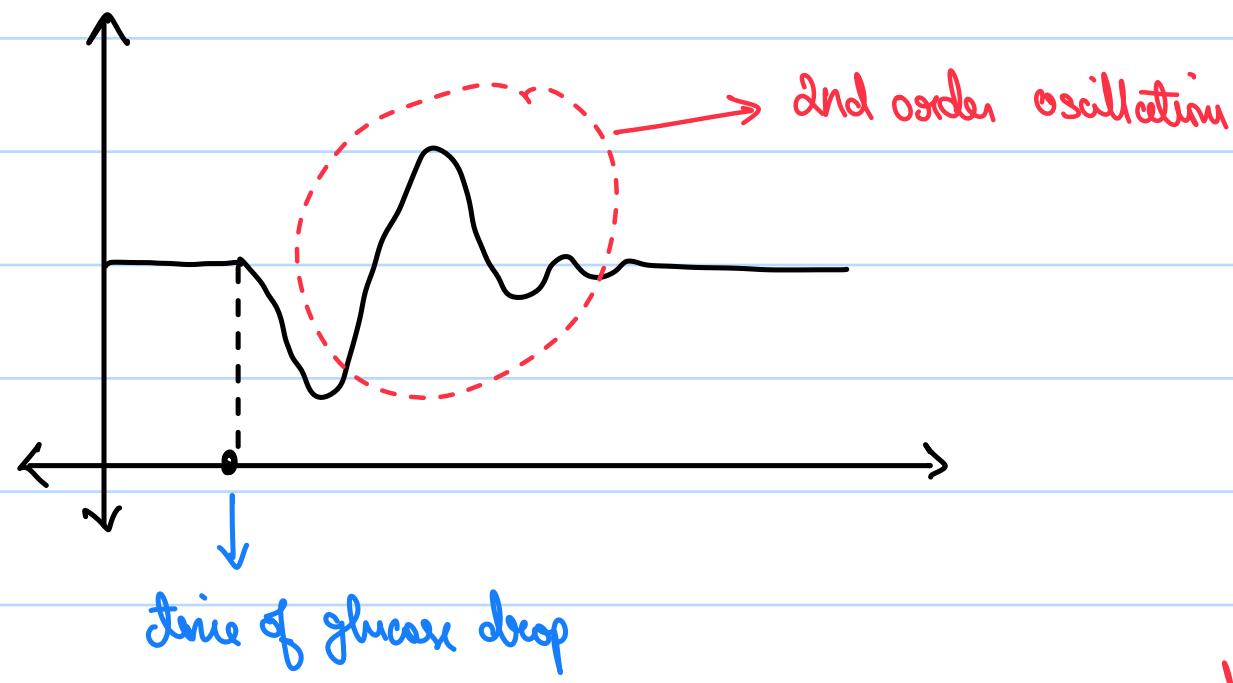
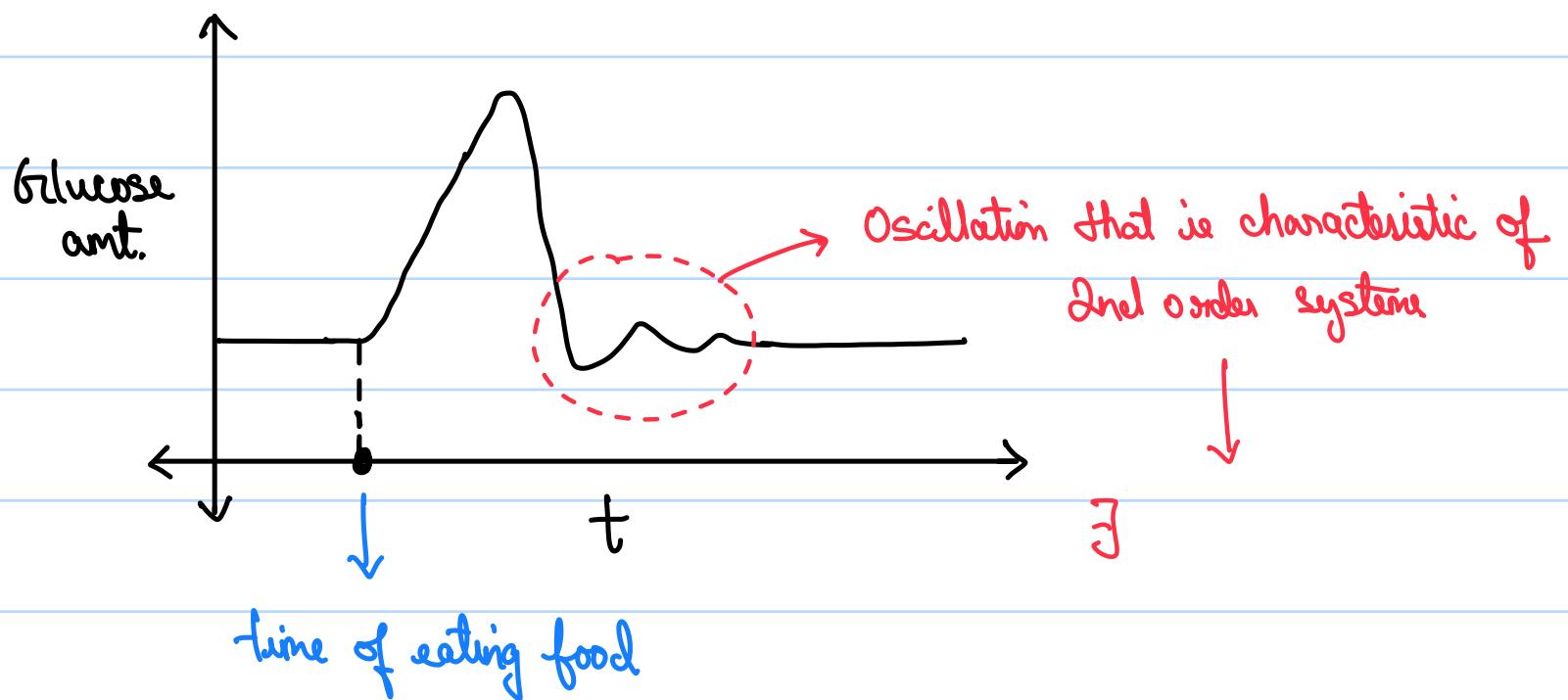
- The decision making of the cell network depends on the design of the network, made through the process of evolution.

- Feedback:

- Most engineering systems employ negative feedback systems, to reduce the steady state error of the system.
- Biological systems employ both negative and positive feedback systems. Positive feedback systems are found as feedthrough systems.



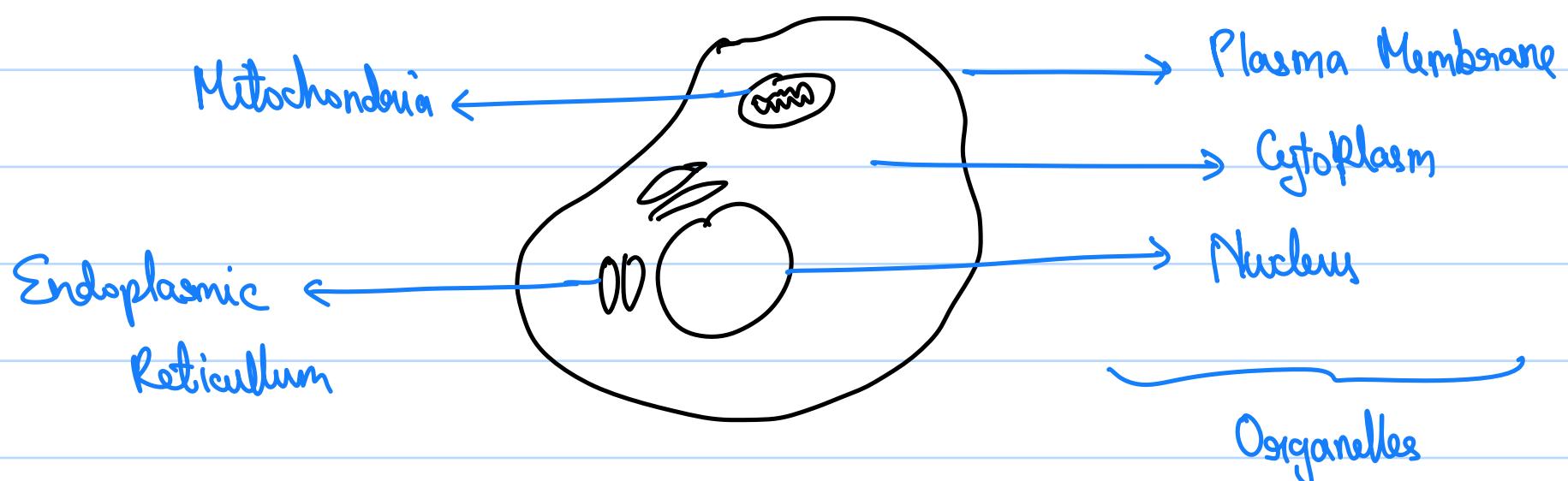
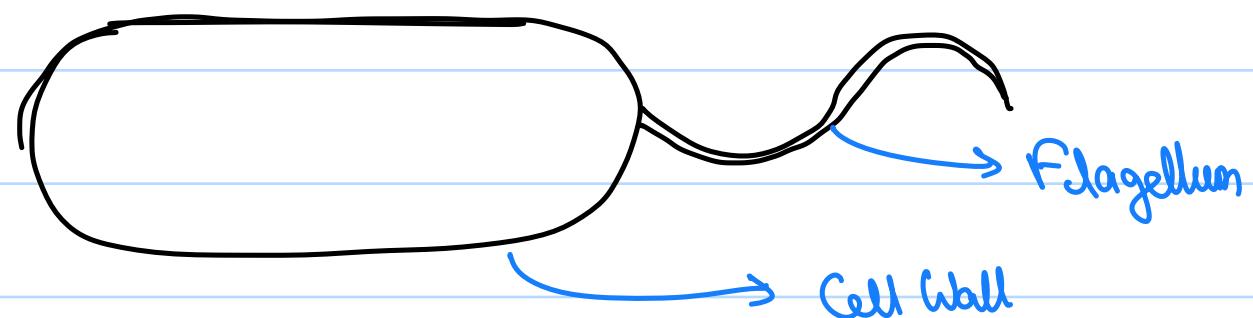
Example: Glucose Homeostatic System.



- Physiology : Study of the system inside a cell .

→ Cells :-

- Cell types : Prokaryote = No nucleus
Eukaryote — Has nucleus
- Prokaryotes have flagella that they use to move, Eukaryotes may not have to move, ie they are static



- Each cell is programmed to respond to specific combination of extra-cellular signals.

◦ Types of Signals :-

- 1) Contact Dependent : Signal due to direct contact of a cell with another, ie like a mechanical signal. Is cutoff when cancer, so signal is not proper.

2) Paracrine: Cell secretes hormone that acts on a select few, local sites

3) Synaptic: Direct cell-to-cell communication (P2P)

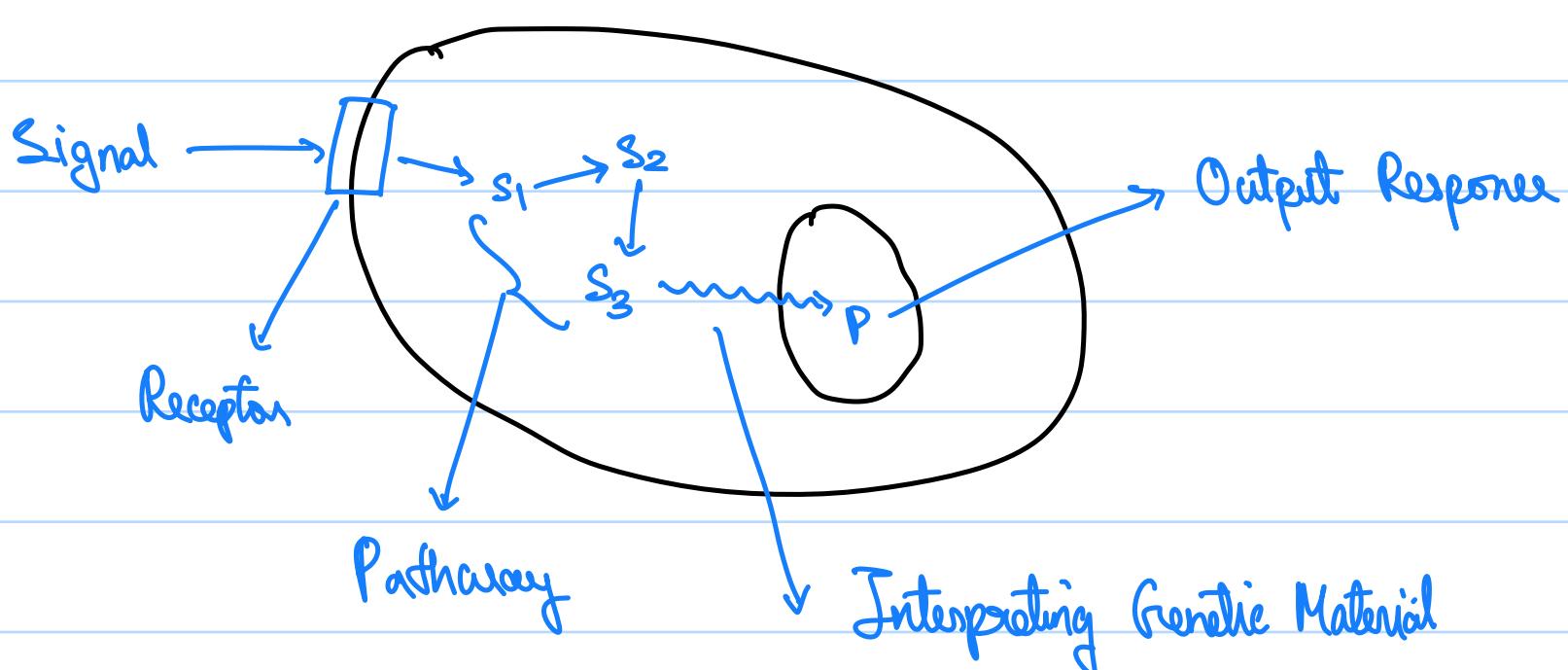
4) Endocrine: Cell secretes hormone that acts on multiple sites

Example: The neurotransmitter acetylcholine is a molecule that decreases the frequency of heart beat in the heart, controls the contraction of muscles in the body and the secretion of saliva in the salivary gland. The same transmitter molecule performs different actions on different sites of the body.

• The processing part of the cell is guided by the genetic material, proteins and metabolites of the cell.

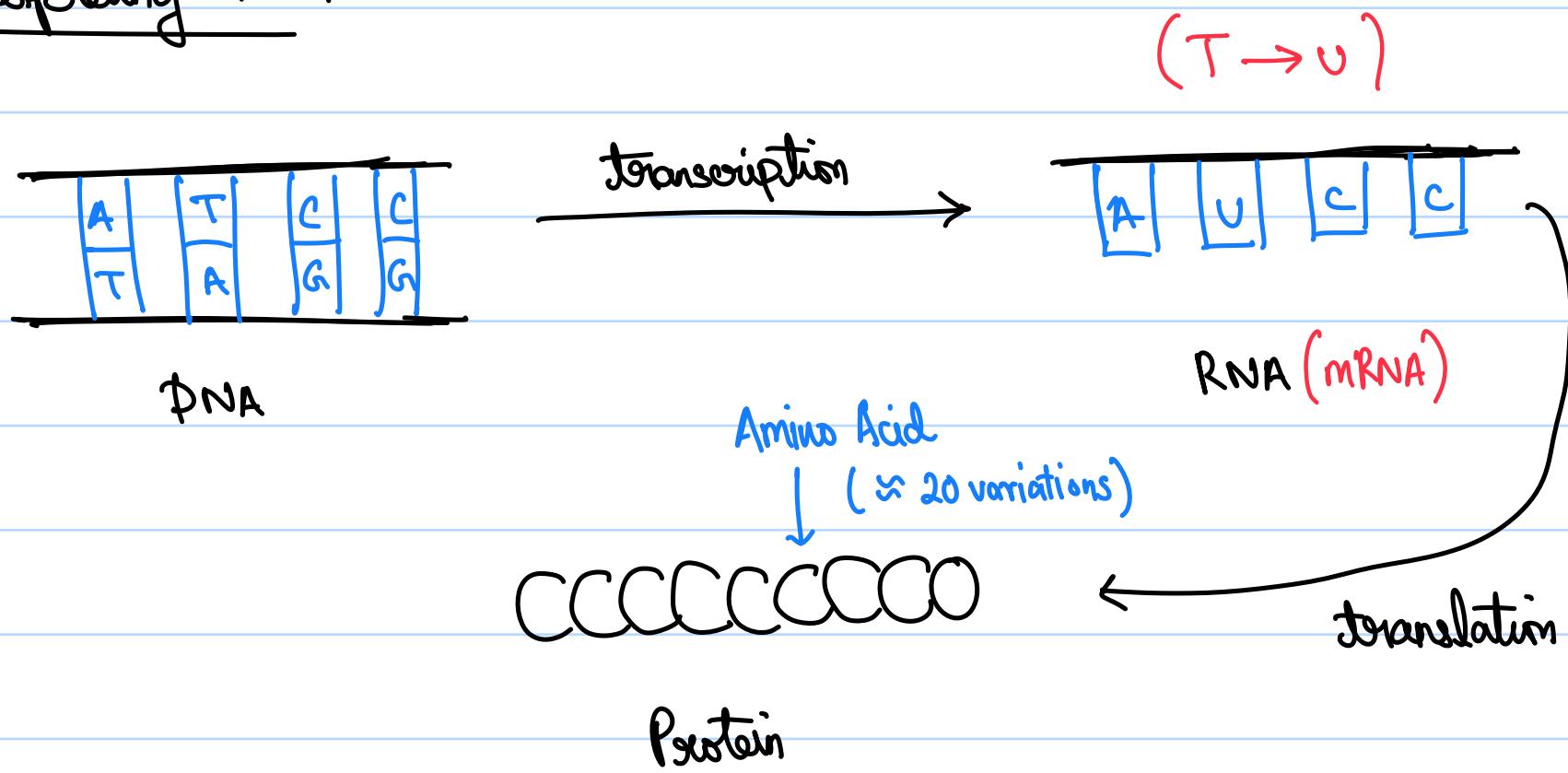
Metabolite: Messenger of the cell (analogous to hormones and the human body).

• To detect a signal, special protein are present on the membrane of the cell.



- The receptor and the hormone combine and form the RL complex (Receptor-Ligand)
- The RL complex triggers a pathway (a series of chemical reactions) which lead to the cell, resulting in a certain final response.
- The receptor proteins and the pathways are programmed in the genetic material of the cell.

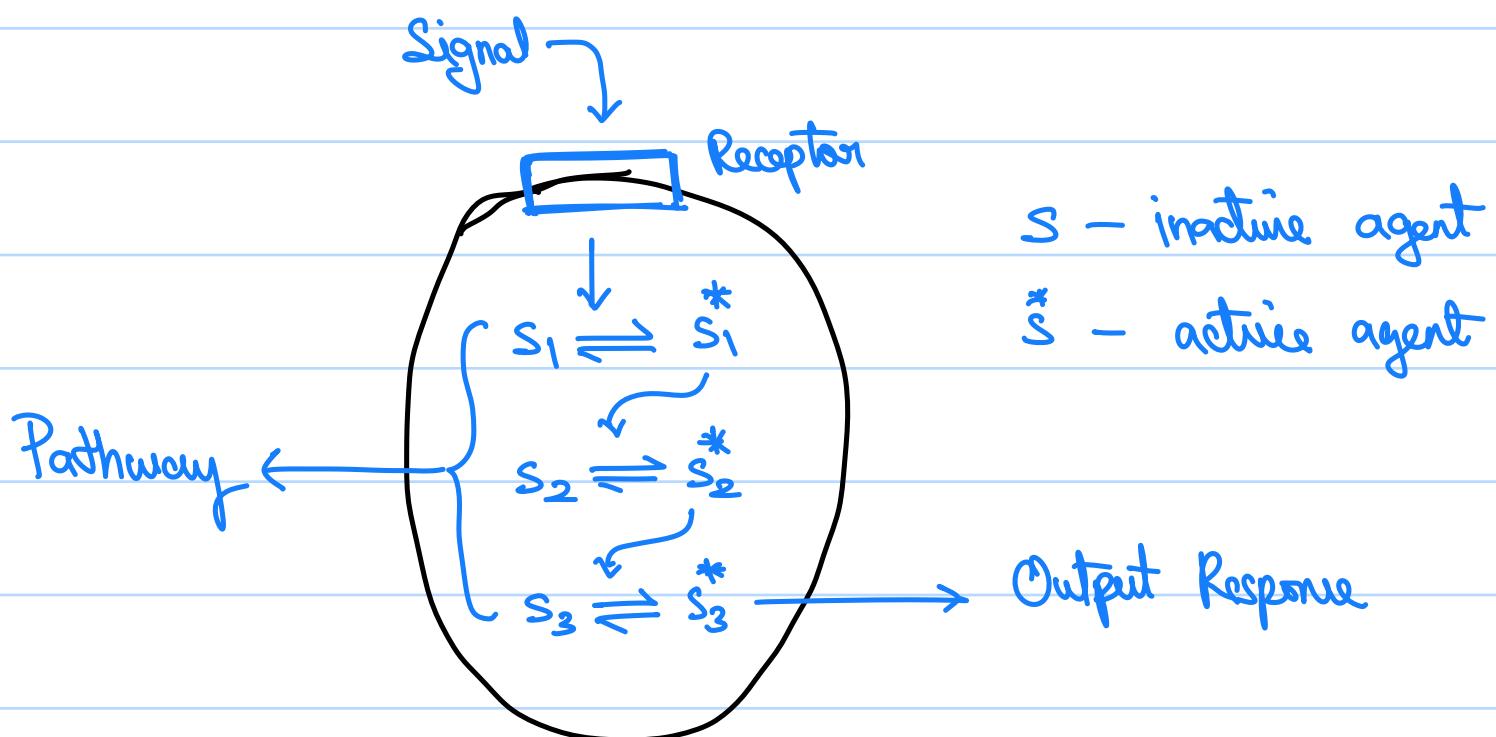
◦ Interpreting DNA:-



- The final response of a hormone is a protein, which goes into the nucleus to read the genetic material (as above), to make new protein as the output response.

- The final response protein to the signal need not access the nucleus always, as that process is time-intensive, is a slow response.

- In a fast response, the output response is generated during the pathway itself.



Mechanism of Fast Response

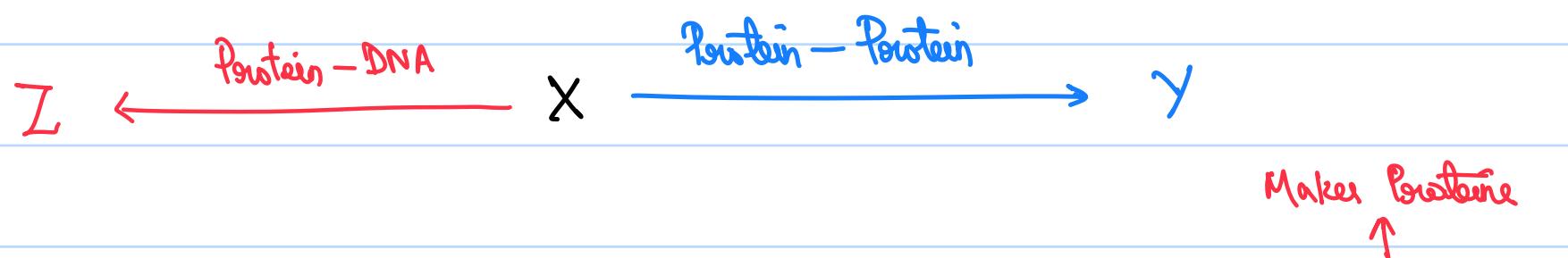
- The protein has a 3D structure, which is governed by non-covalent interactions (hydrogen bonding, Van der Waals forces).

The 3D structure of the protein can change to make it active/inactive.

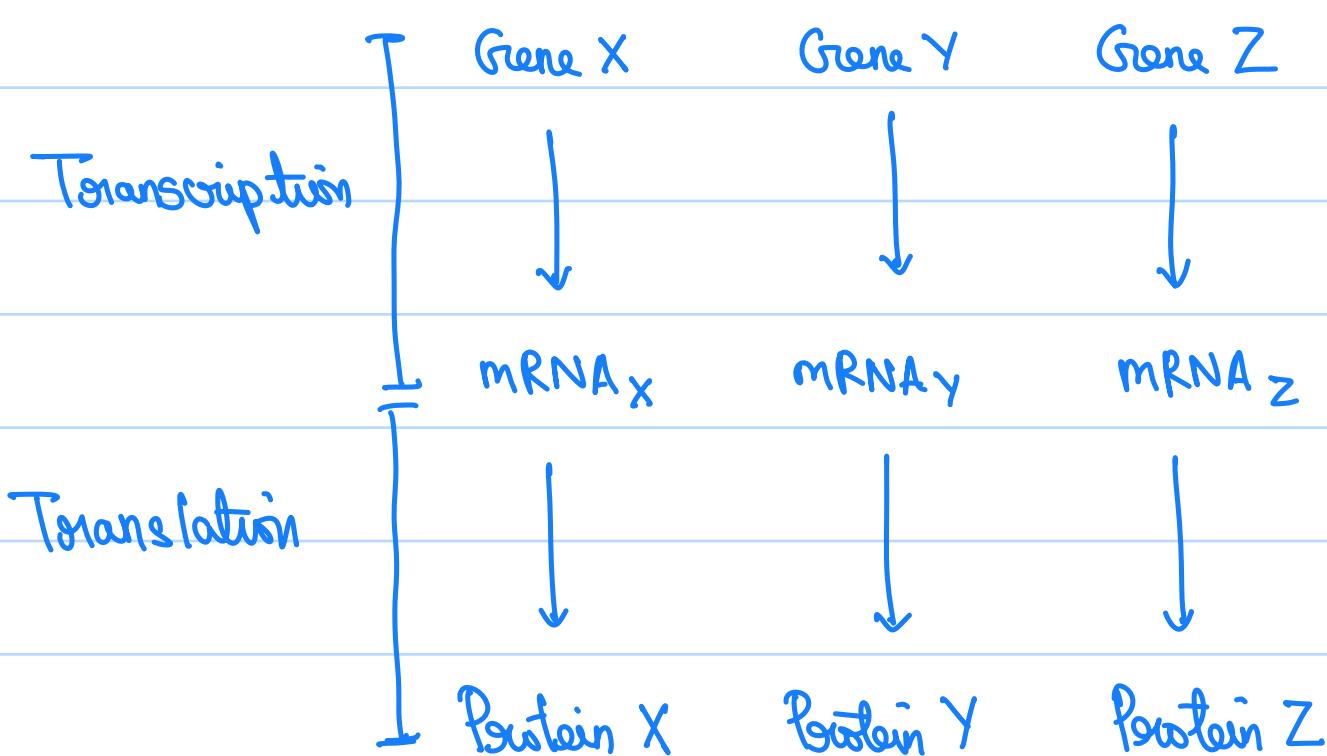
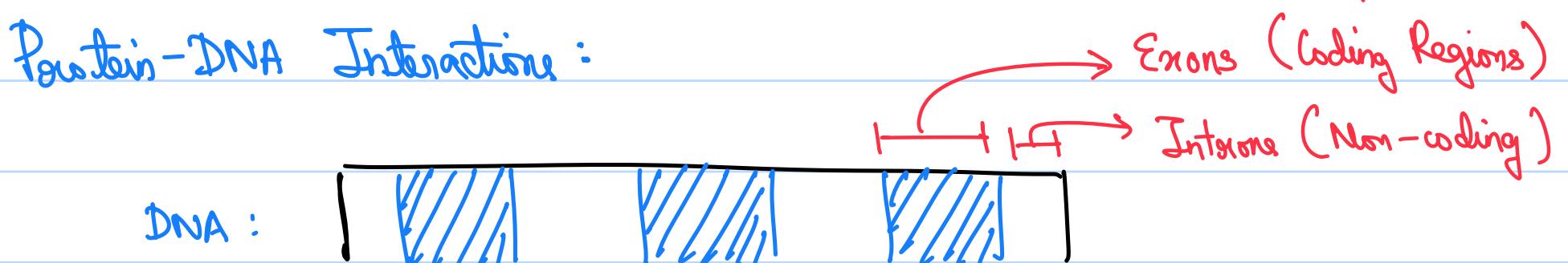


- The behavior of the cell as a system is made up of the following interactions, which make up the network of the system.

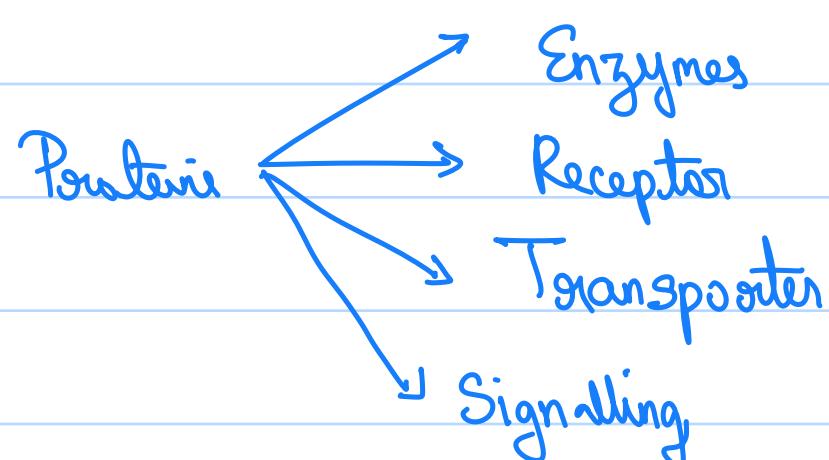
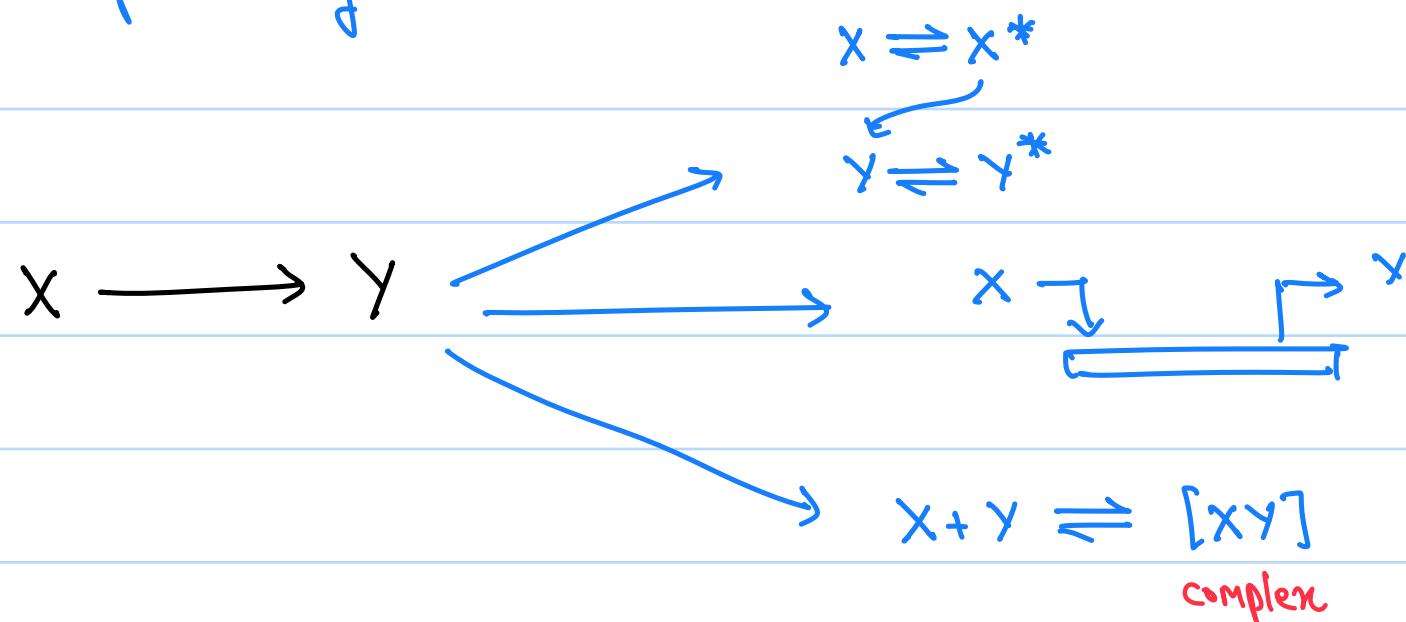
- 1) Protein-Protein interaction
 - 2) Protein-DNA interaction
- } Forms a network in the form
of a directed graph



Protein-DNA Interactions:



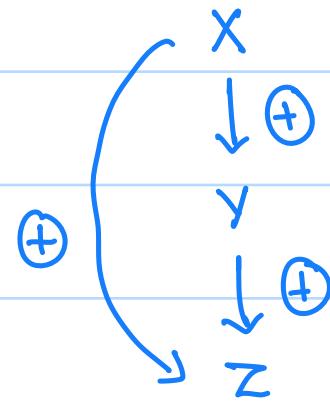
Protein-DNA interactions are much stronger than Protein-Protein interactions as seen previously.



17/10/25

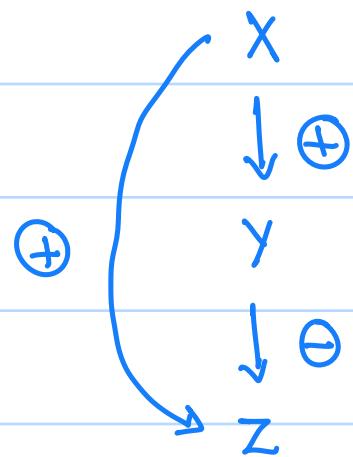
→ Analysis of Sensory Networks :-

◦ Coherent Feed Forward Loop :



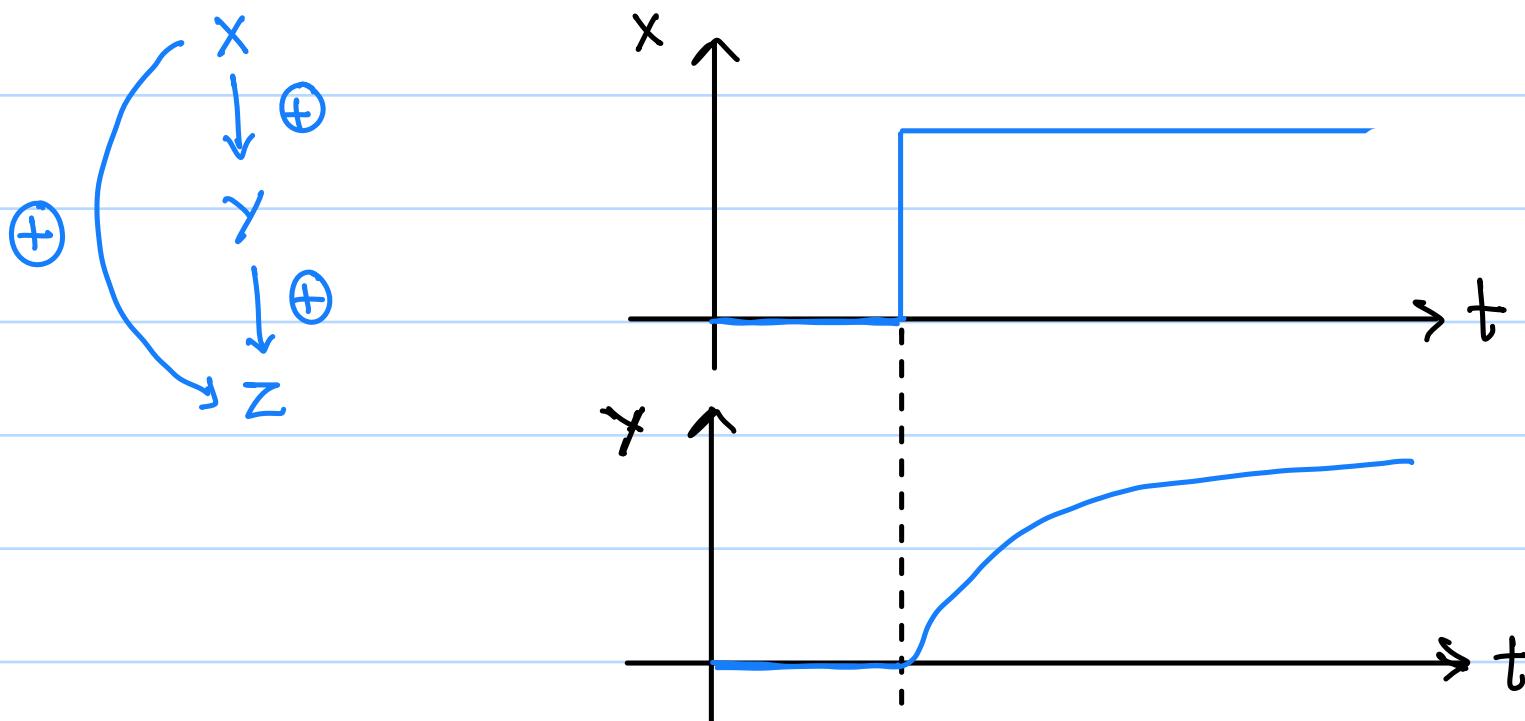
The effect of X on Y is the same as the effect of Y on Z, such a system is said to be coherent.

◦ Incoherent Feed Forward Loop :



The effect of X on Y is not the same as the effect of Y on Z, so the system is said to be incoherent.

In the given coherent system, let x be a step up,



Anish Toshniwal

Subal Manchanda

Sricharan Vinoth Kumar

Swati Yelamanchili

Udhan Malpani

Advaith Sudarshan

Himangi Sahoo

Ritrik Arula

Sanjana Punna

Anushka Saini

Joanna Allu Preetika

Manya Jain

Vedant

Nikhilesh Nallavelli

Pawan

Zope's

Creepy Shit. Not mine.

Gauri Krishnan

z

Summary :-

- 1) Simple System $X \rightarrow Y$,
- 2) Autoregulation (NAR $\begin{array}{c} X \\ \downarrow \\ X \end{array}$, PAR $\begin{array}{c} X \\ \uparrow \\ X \end{array}$)
- 3) FFL (Coherent, Incoherent)

System Thinking - H2

Intro To Systems Biology - Design Principles of Bio. Circuits

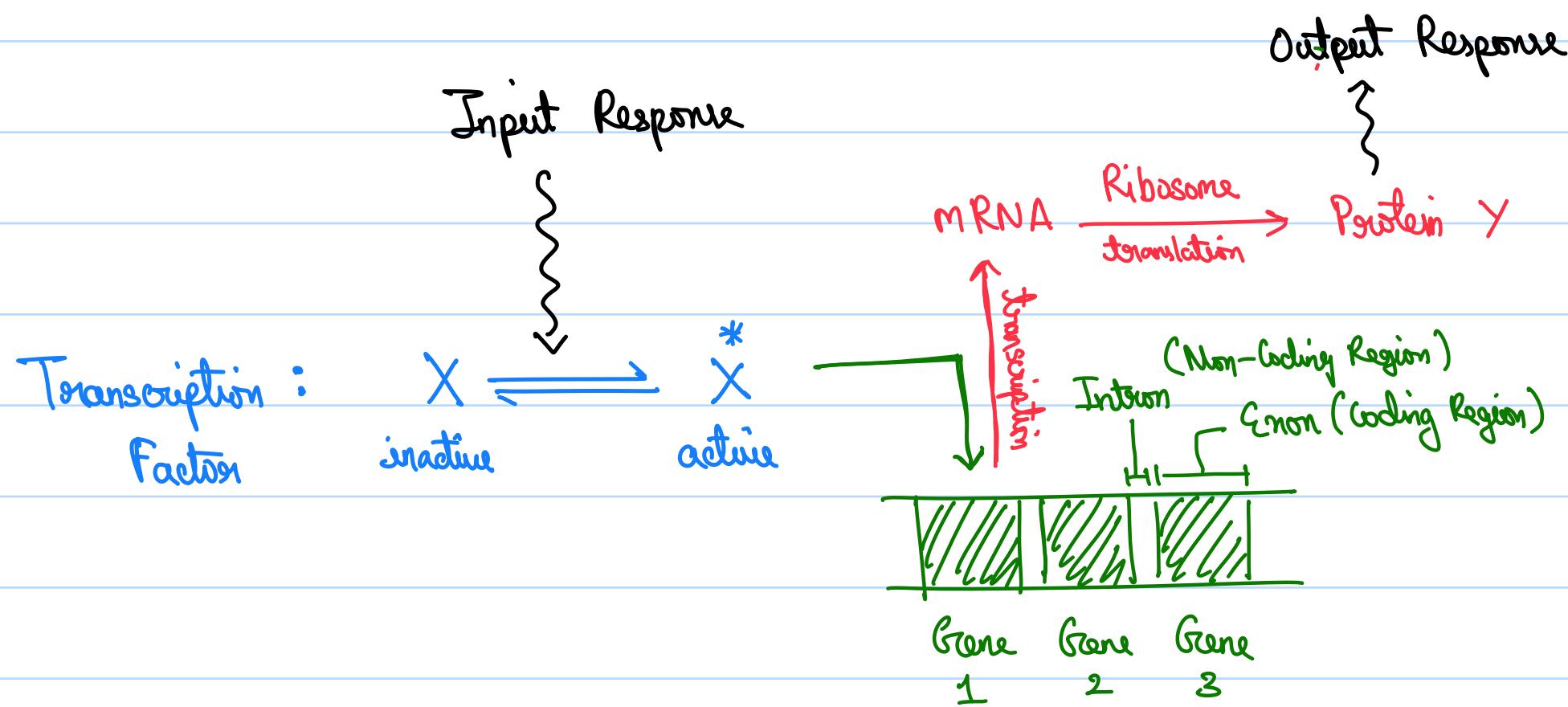
→ Biological Networks :-

- The cell can be thought of as the basic unit of an organism.
- A cell encounters different situations that require the synthesis of different kinds of proteins.
- Each cell has an information processing network that continuously monitors its environment and produce protein accordingly.
- Such an information processing network that determines the rate of synthesis of each protein is termed as a **transcription network**.

→ Transcription Network :-

- Transcription Factors: Proteins that represent the cell's environmental state.
- The Environmental state may be external (temperature, osmotic pressure) or internal (cell damage, metabolite levels)
- Transcription factors switch rapidly between an inactive and active state, depending on the signal input.
- The active transcription factor then binds to the DNA to control the rate of production of a certain protein, by regulating the rate at which the target gene is read.

The target gene is then read (**transcribed**) into mRNA, which is then translated into protein by ribosomes.



- Sometimes the protein Y may itself be another transcription factor that may repeat the above process to create another protein Z.

Input Response $\rightsquigarrow X \rightarrow Y \rightarrow Z \rightsquigarrow$ Output Response

The protein Y is termed as the gene product of Gene 1 (in the fig.)

- The transcription factor affects the rate at which the gene is transcribed into mRNA.

Activator - Increase the transcription rate

Repressor - Decrease the transcription rate

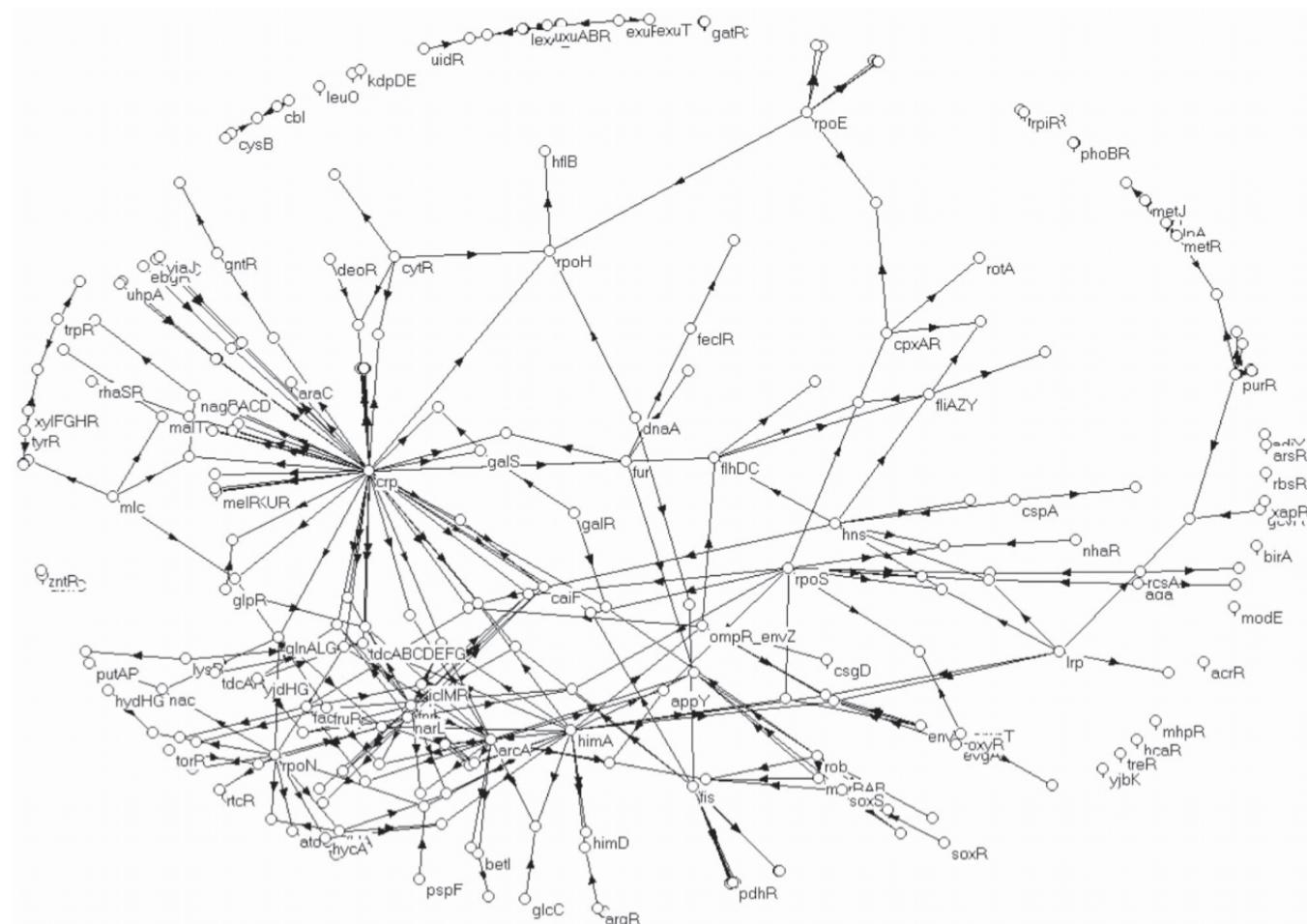
- Since the transcription factors themselves are gene products of some other gene, the total interaction of the transcription factor of a cell can be summarized by the transcription network.

- The transcription network is a Graph, with the nodes as the genes and the edges as the interactions of their gene products.

$X \rightarrow Y \triangleq$ The transcription factor generated by gene X regulates the transcription of gene Y

- The input signals are molecules, proteins or a environmental factor that directly affects one of the transcription factors.

$X \rightarrow Y \rightleftharpoons$ X's gene product is an activator of Y
 $X \rightarrow Y \rightleftharpoons$ X's gene product is a repressor of Y



A Real World Transcription Network

o Timescales:

Signal to Trans. factor $\sim < 1$ second

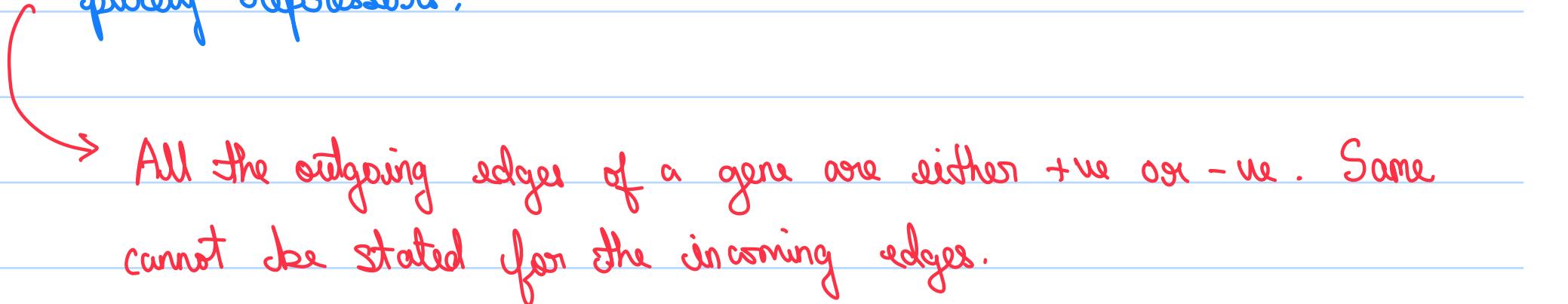
Trans. factor inactive-active equilibrium \rightleftharpoons second

Transcription and Translation in minutes

Accumulation of esp protein v minutes to hours

- Transcription networks are very modular, because of which smaller sections can be isolated and new sections can be added to the network.

- Most trans. factors show only one type of regulation (+ve, -ve) for all their target genes, ie, they are either purely activation or purely repression.

 All the outgoing edges of a gene are either +ve or -ve. Same cannot be stated for the incoming edges.

- Input Function :-

- Say we have $X \rightarrow Y$, ie X is a trans. factor of Y , then the rate of production of Y can be represented as a function of the concentration of $\overset{*}{X}$ (the active form of X), ie,

$$\text{Rate}(Y) = f(\overset{*}{X})$$

$$\Rightarrow \frac{d[Y]}{dt} = f([\overset{*}{X}])$$

$[Y]$ - conc of Y
 $[\overset{*}{X}]$ - conc of $\overset{*}{X}$

- A useful approximation of the function for many real world interaction is the Hill function.

$$f(\overset{*}{X}) = \frac{\beta \overset{*}{X}^n}{K^n + \overset{*}{X}^n} \longrightarrow \text{Hill function of an activation}$$

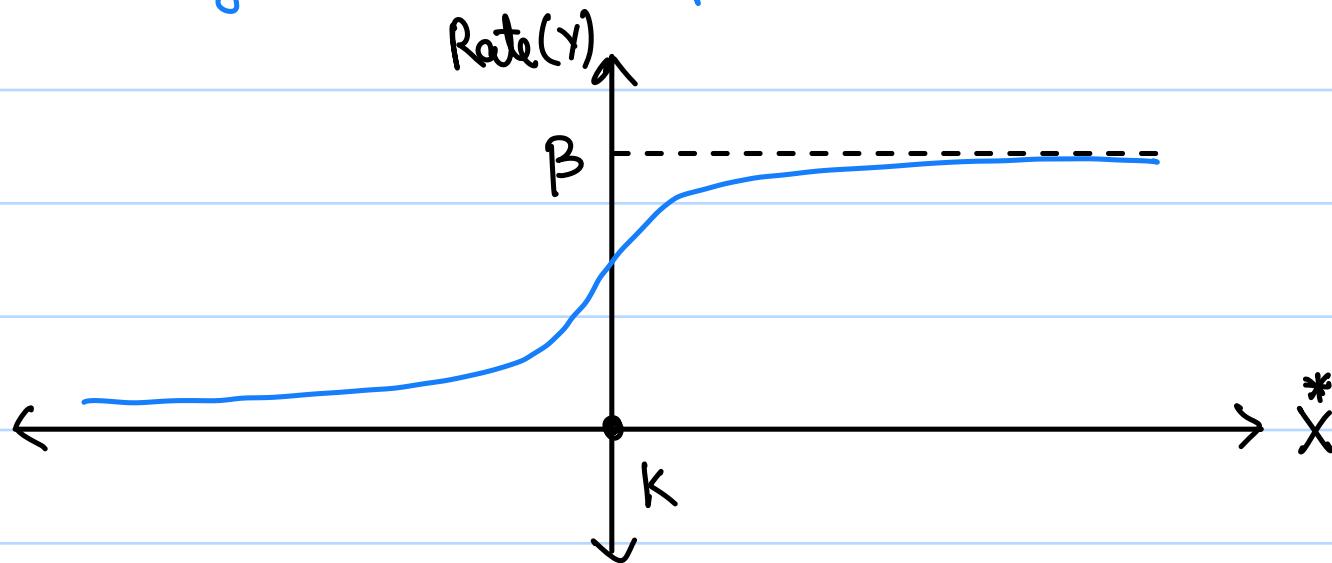
Where,

β - Maximal Expression Level (Determines the saturation conc.)

K - Activation Coefficient (Determines min. $\overset{*}{X}$ conc for significant effect)

n - Hill Coefficient (Determines curve steepness)

- Hill functions give an S-shaped curve as below,

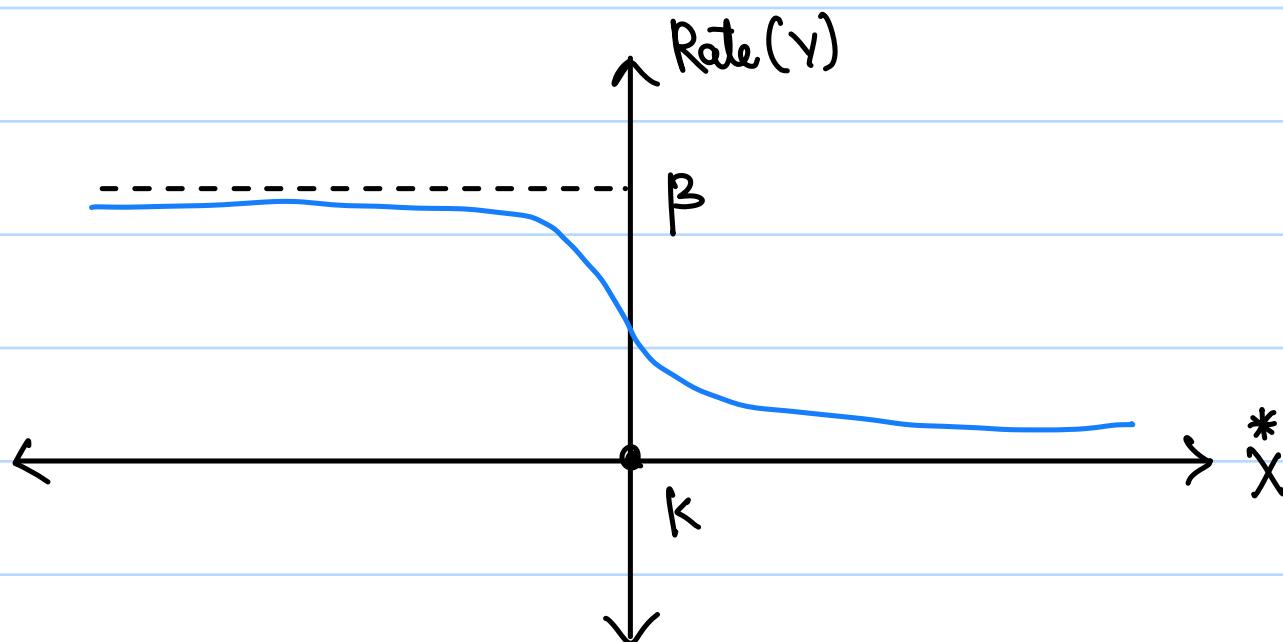


Typical n values are 1-4.

Note: Rate $\hat{=}$ Expression

- For repressors, the Hill function is,

$$f(X^*) = \frac{B}{1 + \left(\frac{X^*}{K}\right)^n} \quad K - \text{Repression Coefficient}$$



Usually K is defined as the concentration of X^* required for 50% of the maximal expression of Y.

- Each edge in the transcription network now also carries three numbers B , K and n .

- Some genes also have a non-zero minimal expression (ie a minimum rate of formation, B_0), also called its basal expression level.
- A simpler approximation for understanding the behaviour of the function, ie it uses binary logic

$$f(x^*) = \begin{cases} B, & x^* > K \\ 0, & x^* \leq K \end{cases}$$

- The above is a step like approximation of the Hill function, often written as,

$$f(x^*) = B \Theta(x^* > K) \quad (\Theta(x^* > K) = \begin{cases} 1, & x^* > K \\ 0, & x^* \leq K \end{cases})$$

- For a multi-input function,

$$\begin{aligned} f(x^*, y^*) &= B \Theta(x^* > K_x \text{ OR } y^* > K_y) \\ (\text{or}) \quad f(x^*, y^*) &= B \Theta(x^* > K_x \text{ AND } y^* > K_y) \end{aligned}$$

Some other functions may have some other condition b/w its inputs (ex: +, *, etc).

- Response Time of the input function :-

- For a single edge in the network, say $X \rightarrow Y$, the concentration dynamics and the response of Y is studied as follows.

- When X is active (ie the conc. of X increases past the threshold), the production of Y happens at a constant rate (β).
- Each protein Y has a degradation / dilution rate α (ie how fast the protein conc. of Y is being reduced), giving Y a net production rate of,

$$\frac{dY}{dt} = \beta - \alpha Y$$

At steady state, $\frac{dY}{dt} = 0$

$$\Rightarrow \alpha Y_{st} = \beta$$

$$Y_{st} = \underline{\frac{\beta}{\alpha}}$$

Now if the production of Y by X stops, ie, β becomes 0, the exponential decay upon solving the DE is given by,

$$Y = Y_{st} e^{-\alpha t}$$

In this decay, the half life $T_{1/2}$ of Y is given by,

$$T_{1/2} = \frac{\log 2}{\alpha}$$

This half life is also termed as the response time of Y .

- A loss of the input signal for X , will lead to an exponential decay of Y as shown above.

Now if $Y = 0$ initially, solving the DE for the growth of Y will give us,

$$Y = Y_{st} (1 - e^{-\alpha t})$$

The rate β affects the steady state concentration, rate α affects the response time of the protein.

- For most proteins, degradation rate is zero. Since dilution depends on the growth of the cell, α_{dl} is the same for most proteins.

$\Rightarrow \alpha \approx$ constant for a cell.

$\Rightarrow \frac{\log 2}{\alpha}$ is constant for a cell. Treated as cell generation (τ).

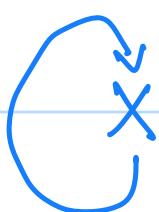
→ Network Motifs :-

- Motifs are patterns / subgraphs that occur more frequently in real world networks, than in a randomized network.
- Biological mutations lead to the deletion of edges, thereby, the destruction of some subgraphs in a trans. network.
- Therefore, if a certain subgraph has survived through multiple

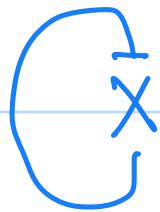
stages and generation of evolution, then it must provide some initial function / property to the full network, hence the need of defining motifs.

- Autoregulation :-

- The regulation of a gene by its own gene product.
- Negative Autoregulation : Repressor genes that repress their own transcription, exhibit negative autoregulation (NAR).
- Positive Autoregulation : Activators that activate their own transcription, exhibit positive autoregulation. (PAR)



PAR



NAR

- NAR and Response Time :-

- Say the gene X undergoes NAR. The dynamics of X are denoted via its production and degradation rates,

$$\frac{dx}{dt} = f(x) - \alpha x$$

- Since X is a repressor of itself,

$$f(x) = \beta(1 - \theta(x > K)) \quad [\theta - \text{Logical Step fn.}]$$

$$\Rightarrow \frac{dx}{dt} = \beta(1 - \theta(x > K)) - \alpha x$$

Assuming $x = 0$ at $t = 0$, initially we have

$$\frac{dx}{dt} = \beta - \alpha x \quad \left. \begin{array}{l} \Rightarrow t = \frac{-1}{\alpha} \ln \left(\frac{\beta - \alpha x}{\beta} \right) \\ \beta e^{-\alpha t} = \beta - \alpha x \\ \Rightarrow x = \frac{\beta}{\alpha} (1 - e^{-\alpha t}) \end{array} \right\}$$

For $x \ll \frac{\beta}{\alpha}$, $x(t) = \beta t$

If $x > K$,

$$\frac{dx}{dt} = -\alpha x < 0$$

Therefore we have,

$$x < K \Rightarrow \frac{dx}{dt} > 0$$

$$x > K \Rightarrow \frac{dx}{dt} < 0$$

From these results we can say that the steady state concentration should be K . ($x_{st} = K$)

- Delays in the system can cause some overshoot and oscillation around $x = K$.

- The response time of X is given as,

$$X(t) = \beta t \Rightarrow \beta T_{1/2} = \frac{X_{st}}{2} = \frac{K}{2}$$

$$\Rightarrow T_{1/2} = \frac{K}{2\beta}$$

- Greater the maximal expression (β), shorter the response time of the gene.
- Therefore, NAR can be used to give a high initial rate of production, then use the autoexpression to stop production at $X = K$.

To show that this is faster than a simply regulated gene
(produced at rate β_{sim} and degraded at rate α_{sim})

$$X_{st} = \frac{\beta_{sim}}{\alpha_{sim}}$$

For comparison, let $K = \frac{\beta_{sim}}{\alpha_{sim}}$

$$T_{1/2 sim} = \frac{\log 2}{\alpha_{sim}}, T_{1/2 NAR} = \frac{K}{2\beta_{NAR}} = \frac{\frac{\beta_{sim}}{\alpha_{sim}}}{2\beta_{NAR}} = \frac{1}{2\alpha_{sim}} \left(\frac{\beta_{sim}}{\beta_{NAR}} \right)$$

$$\Rightarrow \frac{T_{1/2 NAR}}{T_{1/2 sim}} = \frac{1}{2 \log 2} \left(\frac{\beta_{sim}}{\beta_{NAR}} \right)$$

$$\Rightarrow T_{1/2 NAR} = \frac{1}{2 \log 2} \left(\frac{\beta_{sim}}{\beta_{NAR}} \right) T_{1/2 sim}$$

If $\beta_{NAR} > \beta_{sim}$, we get $T_{1/2,NAR} < T_{1/2,sim}$, ie shorter response time.

- A similar analysis can be shown if $f(x)$ is represented as a Hill function.

- In Summary,

Benefit of NAR : High initial production rate and settling at desired steady state.

Having a high β in simple regulation would increase the steady state concentration ($x_{st} = \frac{\beta}{\alpha}$) which would lead to undesirable overexpression.

- NAR and Robustness :-

- The production rate of a gene β is expect to fluctuate due to external condition. (Analogue to the effect of noise in a system)
- The repression threshold K is much more robust since it relies on the chemical properties between the DNA promoter and the transcription protein.
- In simple regulation.

$$x_{st} \propto \beta$$

\Rightarrow Change in β can lead to change in x_{st}

- Since K is more resistant to such changes, in NAR the value of X_{st} is not affected by these fluctuations.
- This makes NAR systems more robust than simple regulation.

- PAR, Response Times and Bi-Stability :-

- PAR is much less common in real world networks than NAR.
- PAR systems show low initial rates of production, but as the concentration of X increases, the rate increases, leading to a concave behavior, with $T_{1/2}$ comparable to simple regulation systems.
- If the concentration of X becomes high enough, the production of X continues even if the initial input signal is cutoff, leading to a permanent ON state. (Bi-Stability)
- PAR is used in slow networks, that are used for long-term actions, like development networks, which require irreversible decisions.
- To show the bi-stability,

$$\frac{dx}{dt} = f(x) - \alpha x$$

(β - Represents PAR)

$$\Rightarrow \frac{dx}{dt} = \beta + \beta x - \alpha x$$

$$= \beta + x(\beta_i - \alpha)$$

Steady State,

$$\beta + x(\beta_i - \alpha) = 0$$

$$x_{st} = \frac{\beta}{\alpha - \beta_i}$$

If $\beta_i < \alpha$, the conc. of X reaches a steady state.

If $\beta_i > \alpha$, since conc. cannot be -ve, X does not have any steady state.

$$\frac{dx}{dt} = \beta + x(\beta_i - \alpha)$$

$$dt = \int \frac{dx}{x(\beta_i - \alpha) + \beta}$$

$$t = \frac{1}{\beta_i - \alpha} \ln(x(\beta_i - \alpha) + \beta)$$

$$e^{(\beta_i - \alpha)t} = x(\beta_i - \alpha) + \beta$$

$$\Rightarrow x(t) = \frac{e^{(\beta_i - \alpha)t}}{\beta_i - \alpha} - \frac{\beta}{\beta_i - \alpha}$$

$$x(t) = \frac{\beta}{\alpha - \beta_i} - \frac{e^{(\beta_i - \alpha)t}}{\alpha - \beta_i}$$

$$\text{If } \beta_i < \alpha, \quad x_{st} = \frac{\beta}{\alpha - \beta_i}$$

$$x(T_{1/2}) = \frac{\beta}{2(\alpha - \beta_i)}$$

$$\Rightarrow \frac{\beta}{2(\alpha - \beta_1)} = \frac{\beta}{\alpha - \beta_1} - \frac{e^{(\beta_1 - \alpha)T_{1/2}}}{\alpha - \beta_1}$$

$$\frac{\beta}{2} = \beta - e^{(\beta_1 - \alpha)T_{1/2}}$$

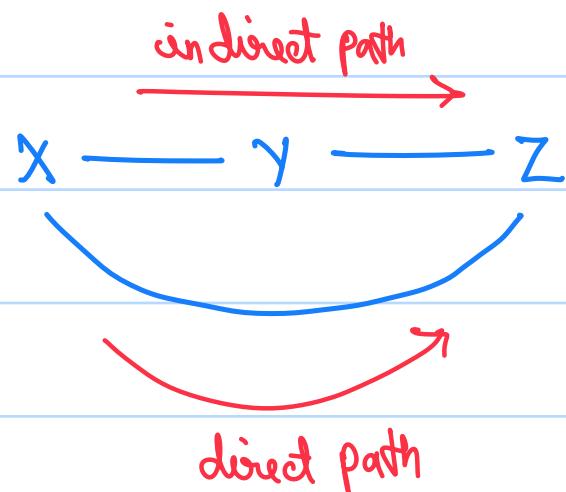
$$\frac{\beta}{2} = e^{(\beta_1 - \alpha)T_{1/2}}$$

$$\log \frac{\beta}{2} = (\beta_1 - \alpha) T_{1/2}$$

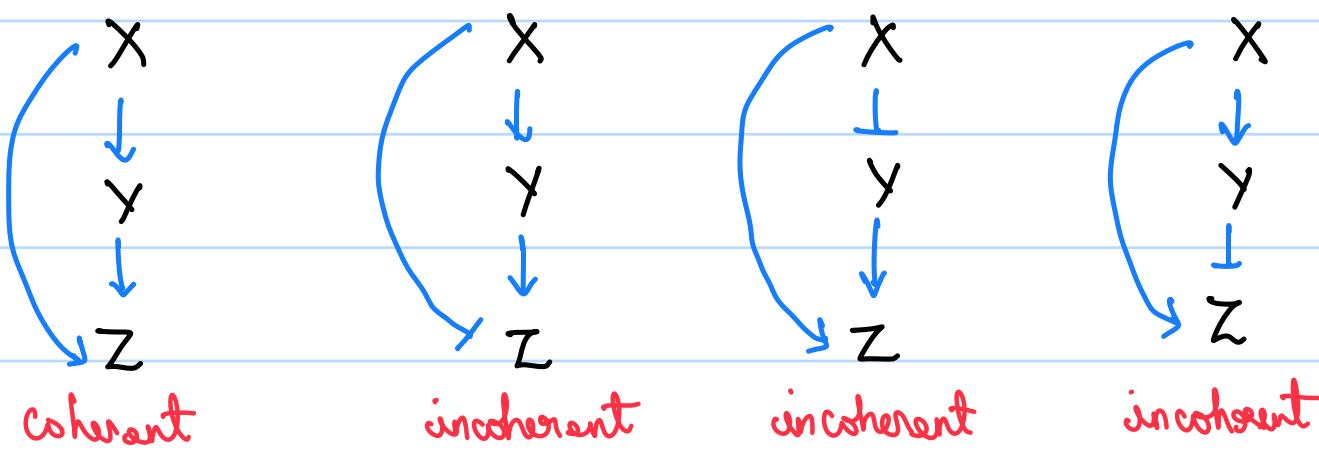
$$\Rightarrow T_{1/2} = \frac{\log \frac{\beta}{2}}{\beta_1 - \alpha}$$

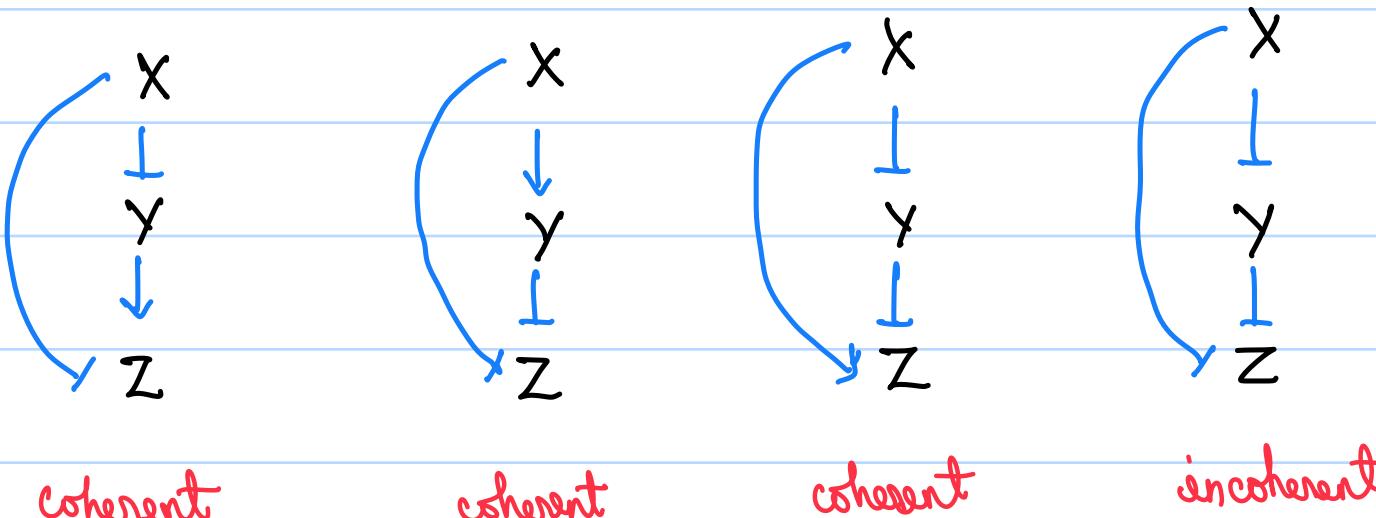
• Feed Forward Loops :-

- FFL is a 3 node network motif.



- If the direct and indirect paths have the same overall regulation type; the FFL is said to be coherent. Else it is incoherent



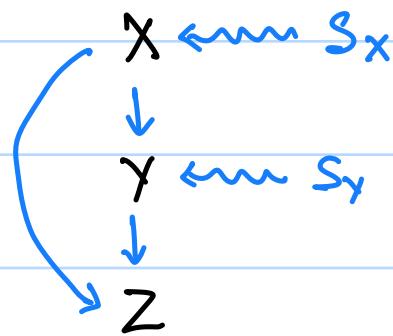


All Possible FFL Configuration

- The expression of Z may need both X and Y to cross some threshold ($\Theta(X > K_x \text{ AND } Y > K_y)$) or just one ($\Theta(X > K_x \text{ OR } Y > K_y)$), giving us a total of 16 possible FFLs, considering the ifp function as well.

- Dynamics of a Coherent FFL with AND Logic :-

- The most common FFL is the Coherent FFL with all edges true, ie,



- Say we have this FFL and Z follows AND Logic, the dynamics of this FFL are as below.

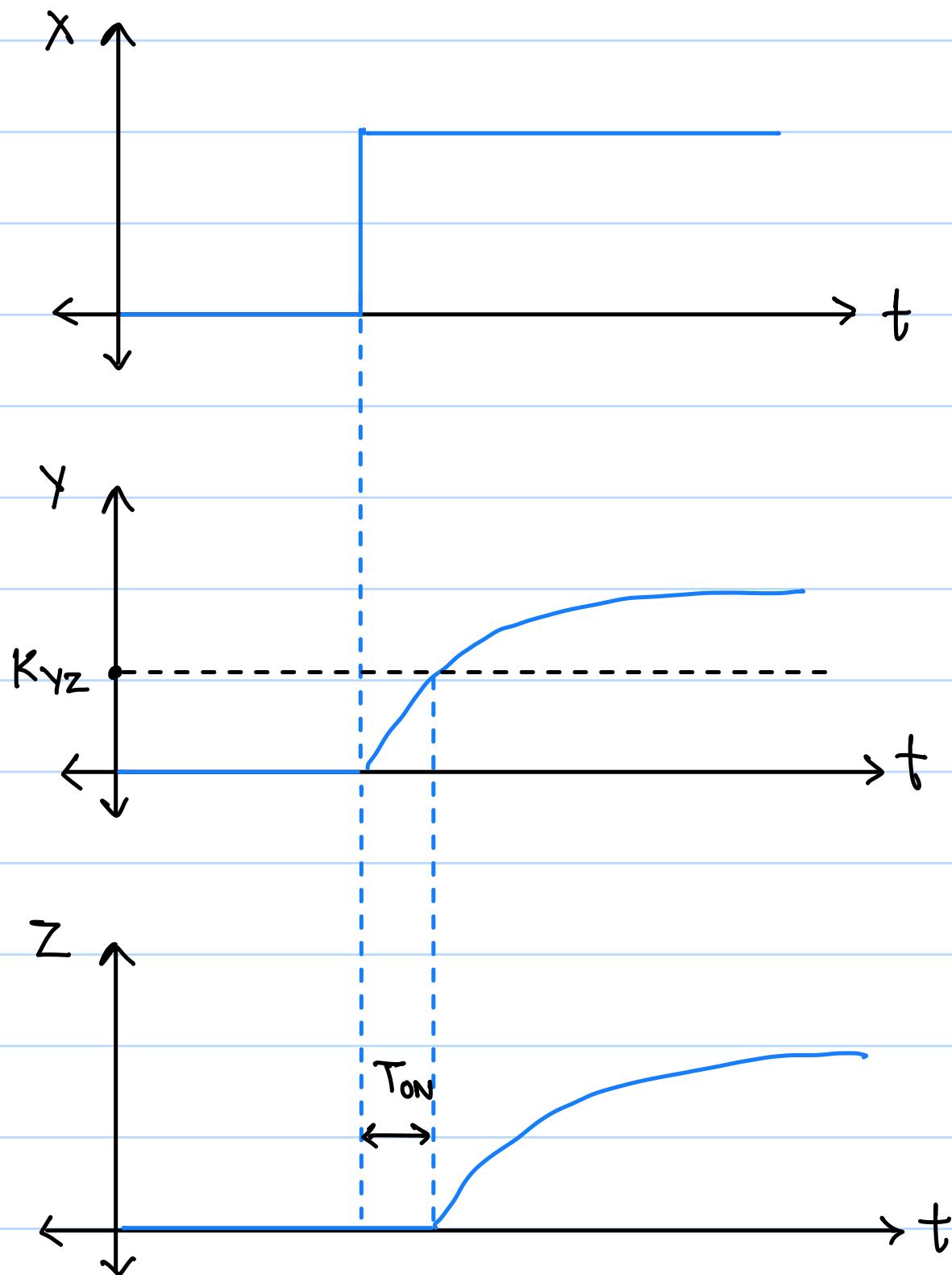
Say X follows a step-like simulation by S_x , then we have,

$$\frac{dY}{dt} = \beta \Theta(X > K_{xy}) - \alpha_y Y$$

and since Z is governed by the AND function,

$$\frac{dZ}{dt} = \beta \Theta(Y > K_{YZ}) \Theta(X > K_{XZ}) - \alpha_Z Z$$

Using these signs, the conc.s can be plotted as,



- As seen above, there is a delay of T_{ON} between the step input activation and the start in production of Z. This T_{ON} is given by,

$$\frac{dY}{dt} = \beta \Theta(X > K_{XY}) - \alpha_Y Y$$

After the step activation,

$$\frac{dy}{dt} = \beta - \alpha_y Y$$

$$\Rightarrow t \int_0^t dt = \int_0^{Y(t)} \frac{dy}{\beta - \alpha_y Y}$$

$$= t = (\ln(\beta - \alpha_y Y) - \ln \beta) \frac{1}{-\alpha_y}$$

$$-\alpha_y t = \ln \left(\frac{\beta - \alpha_y Y}{\beta} \right)$$

$$e^{-\alpha_y t} = 1 - \frac{\alpha_y}{\beta} Y$$

$$\Rightarrow Y = \frac{\beta}{\alpha_y} (1 - e^{-\alpha_y t})$$

$$\Rightarrow Y = Y_{st} (1 - e^{-\alpha_y t}) \quad [\text{As seen before}]$$

$$\text{For } Y = K_{xy}, \quad K_{xy} = Y_{st} (1 - e^{-\alpha_y T_{on}})$$

$$e^{-\alpha_y T_{on}} = 1 - \frac{K_{xy}}{Y_{st}}$$

$$T_{on} = \frac{-1}{\alpha_y} \log \left(\frac{Y_{st} - K_{xy}}{Y_{st}} \right)$$

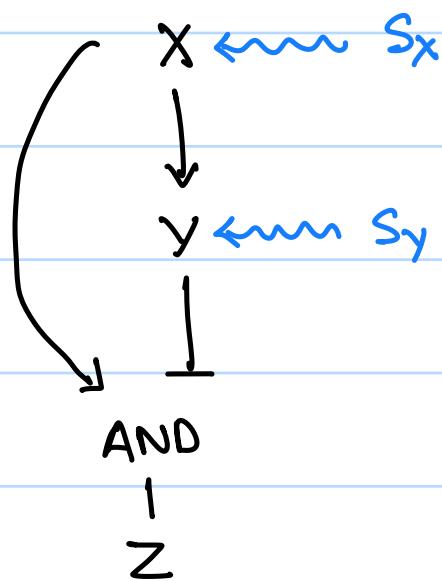
$$\Rightarrow T_{on} = \frac{1}{\alpha_y} \log \left(\frac{Y_{st}}{Y_{st} - K_{xy}} \right)$$

For good performance, we will need K_{xy} significantly lower than Y_{st} .
(For robustness as well, since Y_{st} is vulnerable to fluctuations).

- Also, since Z follows AND logic, there will be no OFF delay in the FFL, since the production of Z ceases when X is absent.
- This behavior of having non-zero ON delay and zero OFF delay is termed as sign-sensitive delay. They can help against input fluctuation.
- This type of FFL being studied here is termed as a persistence detector as it can detect signals present for a finite duration (longer than T_{ov}).
- Using a similar analysis we can see that if Z is governed by an OFF logic, then the system will have zero ON delay and a finite OFF delay.

- Dynamics of an Incoherent FFL :-

- The second-most common FFL is the incoherent FFL shown below,



- Here, the direct path activates Z and the indirect path represses Z . Such an FFL can act like a pulse generator.

- Say X follows a step input, then

$$\frac{dy}{dt} = \beta_y - \alpha_y y$$

$$\Rightarrow y(t) = y_{st} (1 - e^{-\alpha_y t})$$

While $y < K_{yz}$,

$$\frac{dz}{dt} = \beta_z - \alpha_z z$$

$$\Rightarrow z(t) = z_{st} (1 - e^{-\alpha_z t})$$

The production of z late unit Y crosses K_{yz} , which is given by,

$$T_{rep} = \frac{1}{\alpha_y} \log \left(\frac{y_{st}}{y_{st} - K_{yz}} \right)$$

After T_{rep} ,

$$z(t) = z_{st} (1 - e^{-\alpha_z T_{rep}}) = z_0$$

Let the new steady state be z_{st}' , then

$$\frac{dz}{dt} = -\alpha_z (z - z_{st}')$$

$$\Rightarrow z(t) - z_{st}' = C e^{-\alpha_z t}$$

Solving for C by using $t = T_{\text{trap}}$

$$Z_0 - Z_{st}^I = C e^{-\alpha T_{\text{trap}}}$$

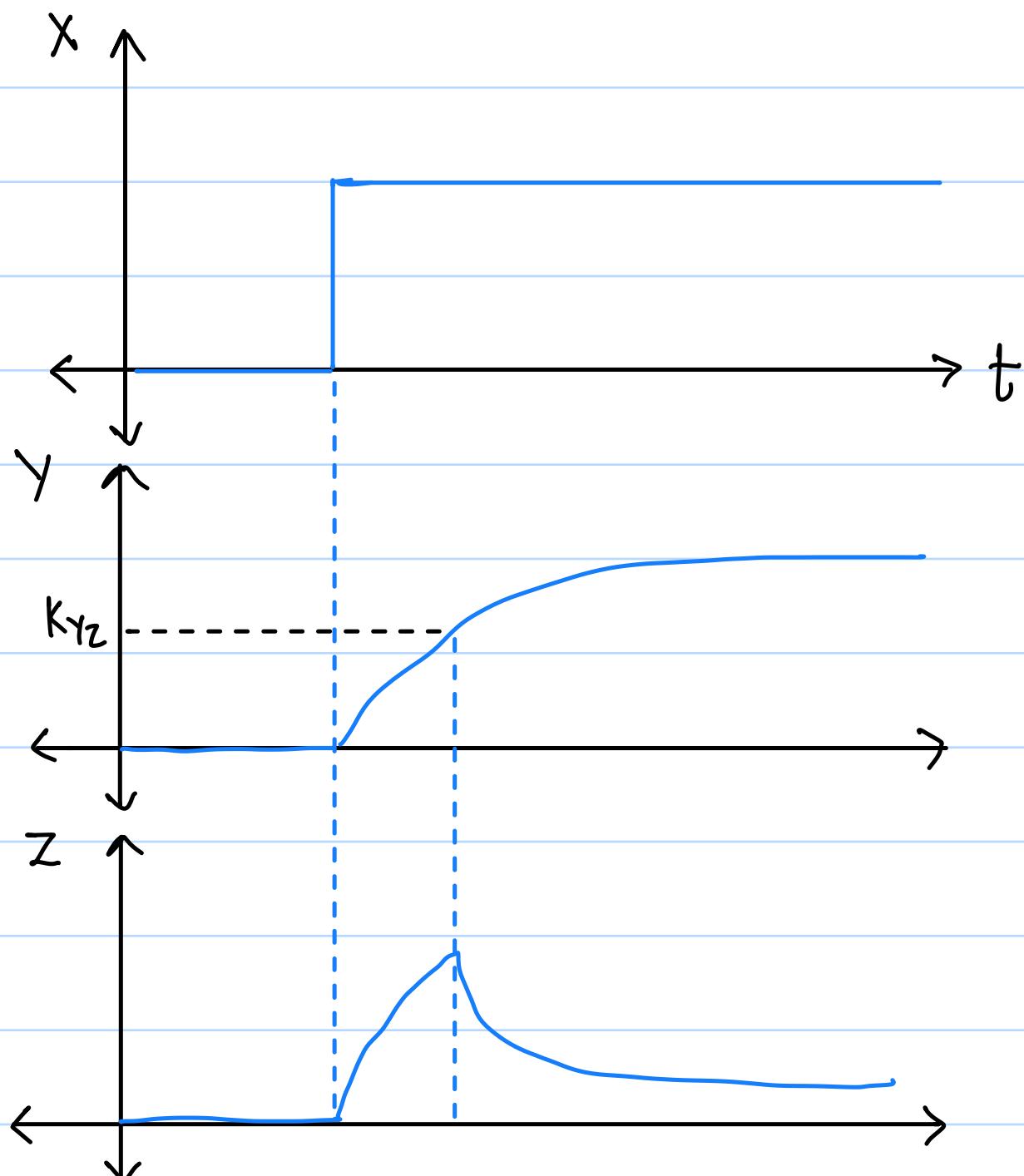
$$\Rightarrow C = (Z_0 - Z_{st}^I) e^{\alpha T_{\text{trap}}}$$

$$\Rightarrow Z(t) - Z_{st}^I = (Z_0 - Z_{st}^I) e^{\alpha T_{\text{trap}}} e^{-\alpha t}$$

$$\Rightarrow Z(t) = Z_{st}^I + (Z_0 - Z_{st}^I) e^{-\alpha(t - T_{\text{trap}})}$$

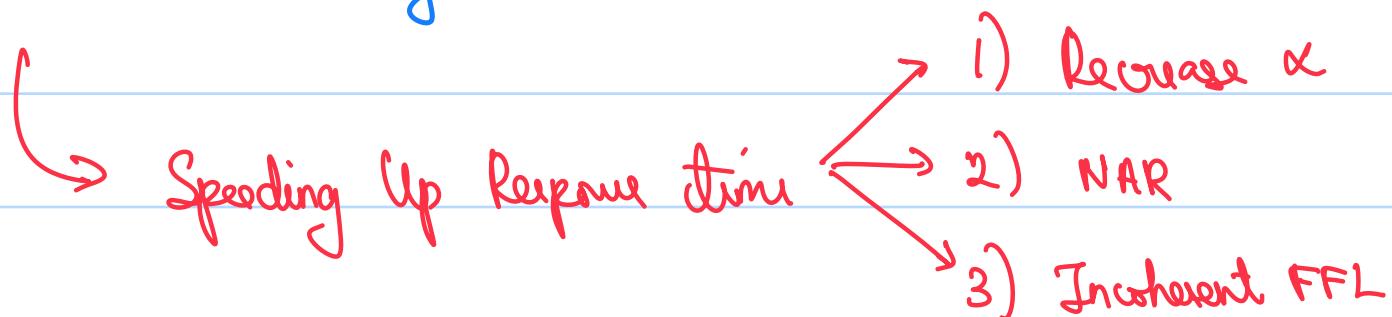
The new steady state Z_{st}^I is given by $Z_{st}^I = \frac{\beta z^I}{\alpha}$, where βz^I is the net basal implosion rate.

$$\frac{Z_{st}}{Z_{st}^I} = \frac{\beta z}{\beta z^I} = F \quad (\text{repression factor})$$



As F increases the repression part of Z becomes more steeper.
At $F \gg 1$, Z acts like a pulse.

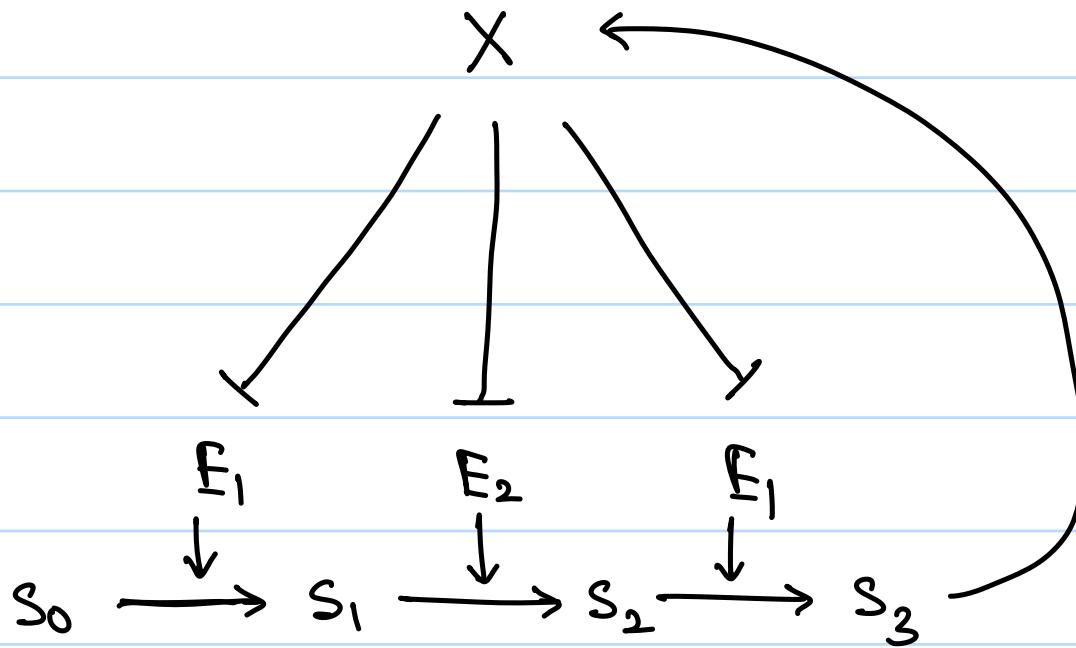
Since the production rate of Z initially is very high, it can be used to speed up the response time of the system, without overexpression at steady state.



- Single - Input Modules :-

A motif in which a single regular gene controls a group of genes.

- A SIM can create a temporal programme of expression (genes are activated one-by-one in a well defined order)
- Each of the target genes usually has only one input, and the master transcription factor shows autoregulation.
- SIMs regulate the genes used in a metabolic pathway, where sequential work is needed to assemble a protein (assembly line)
- SIMs are also used in the response of a general stimuli (DNA damage, heat shock, etc) where it can control genes which individually specialize in one factor of that stimuli.

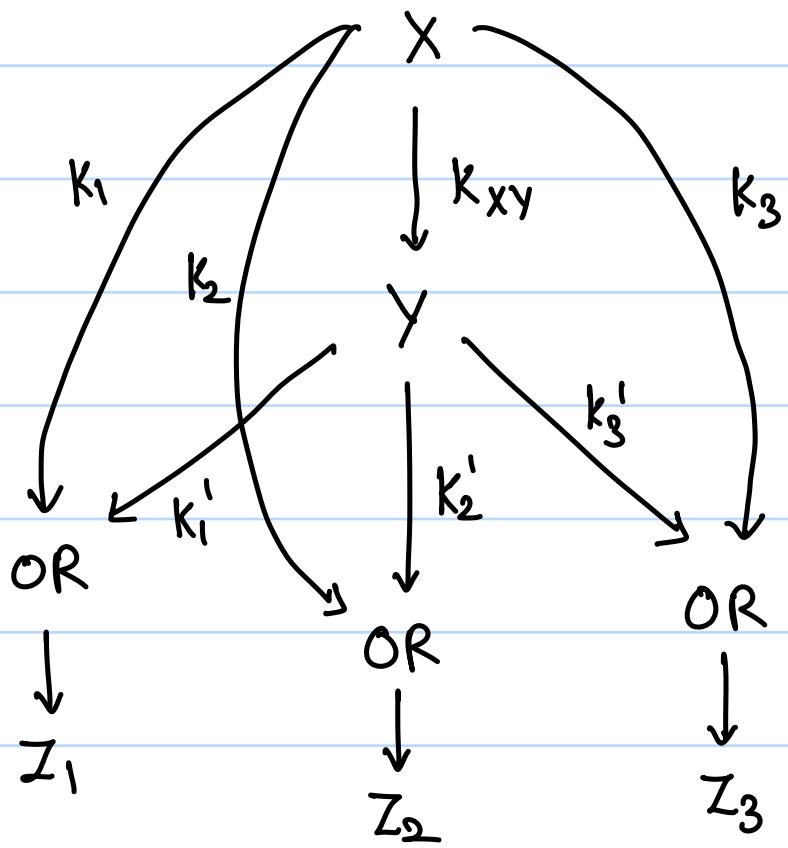


Above is an example of a 3 step metabolic pathway of S_0 to S_3 .

As each step finishes, X represses that particular factor in a temporal order of E_1, E_2, E_3 . Then S_3 activates X which increases the repression even further (−ve feedback loop)

- Temporal Program of Expression :-

- One way of creating a temporal program is by having different threshold levels of X for each target gene I .
- As X increases, one by one the target genes are ON. As X decrease the temporal program follows a generic order. This is termed as Last-In-First-Out order. (LIFO)
- To create a FIFO order, we can use a multi-output FFL, as shown below,



(Found in the flagella system of E. coli)

The ON order is determined by the time X crosses K_1, K_2, K_3 , similar to LIFO.

In the OFF order, as the production of X stops, since Y is still present, the OFF orders are determined by Y.

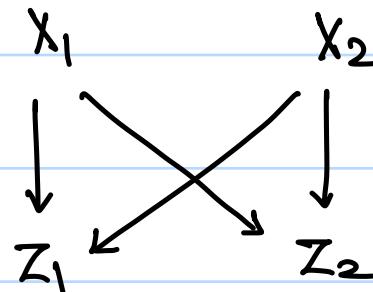
i.e., if $K_1 < K_2 < K_3$ then $K_1' > K_2' > K_3'$ will give us FIFO order.

Such a multi-output FFL can also make the output resilient to fluctuation in X, that can occur due to environmental factors.

The OFF order is done only when X is low for a finite amount of time, making this motif a persistence detector as well.

- Dense Overlapping Regions :-

Uses an array of regulators instead of a single master transcription factor.



- The above DOR is termed as a bi-fan, where 2 trans. factors jointly control 2 target genes.
- The wiring in a DOR is more complicated and dense than the earlier motifs, hence the name.
- A DOR can be thought of as a combinational logic device.

→ Developmental Transcription Network :-

- The above seen motifs and dynamics are mostly designed to respond rapidly to the environment, ie a sensory transcription network.
- Developmental networks govern processes that are long-term and usually irreversible, operating on timescales of days, months and years.
- Developmental networks use few additional motifs that are not commonly found in sensory networks.

- 2-Node Positive Feedback Loops for Decision Making :-

(double +ve)

(double -ve)

- Motifs of 2 TFs that either activate each other or repress each other.

- The double +ve feedback loop has 2 steady states.

- 1) X and Y are both ON, ie they enhance each other's production.
- 2) X and Y are both OFF

Any signal that makes the conc. of X or Y non-zero, can inevitably lock the system irreversibly in the ON state.

This type of behavior is termed as a lock-on mechanism.

- The double negative feedback loop also has 2 steady states

- 1) X is ON and Y is OFF
- 2) X is OFF and Y is ON

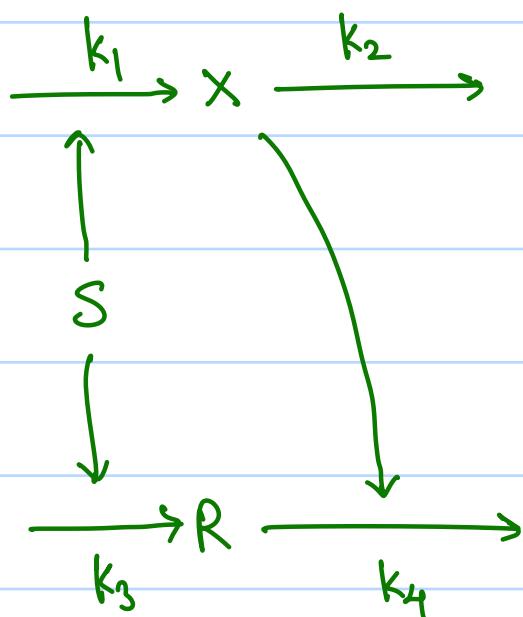
Since one gene always represses the other.

Such a system is useful when X and Y denote 2 very different responses for the cell.

- Often in such a 2 node feedback loop, X and Y each have PAR that enhances the production of the trans-factor, improving the stability of the ON state.

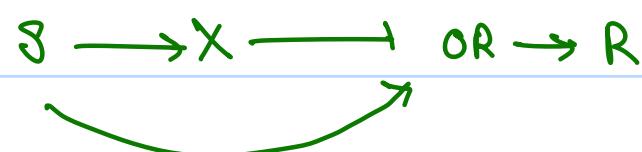
- Such bi-stable states enable the cell to make irreversible decisions.

Example:

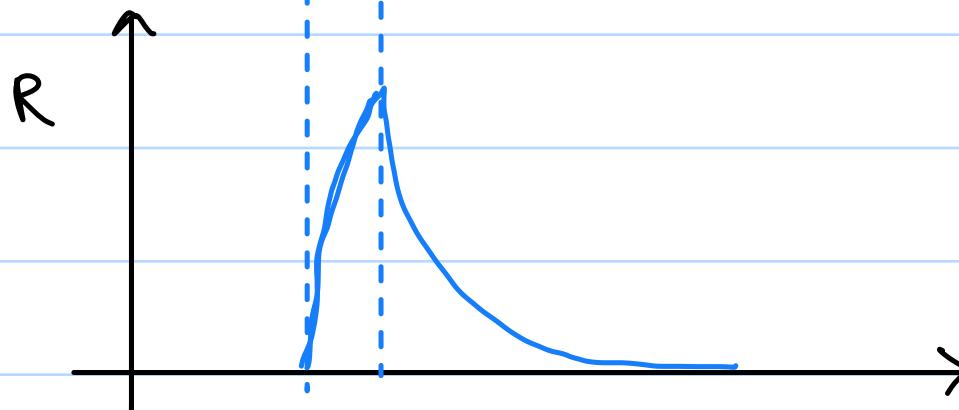
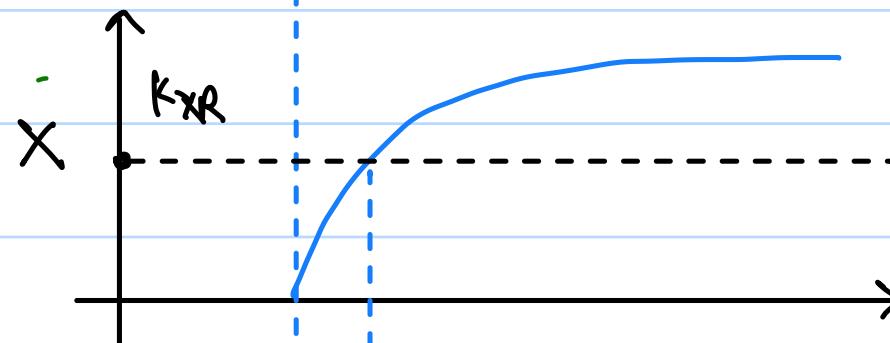
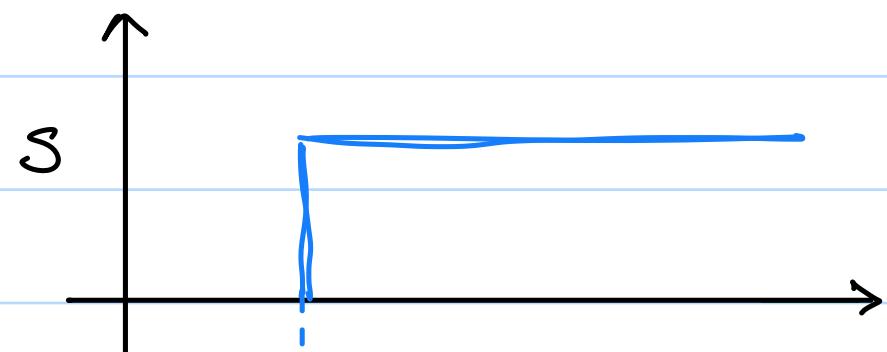


Analyse the dynamics of this circuit.

The given circuit is an example of an incoherent FFL of the form:



This acts like a pulse generator



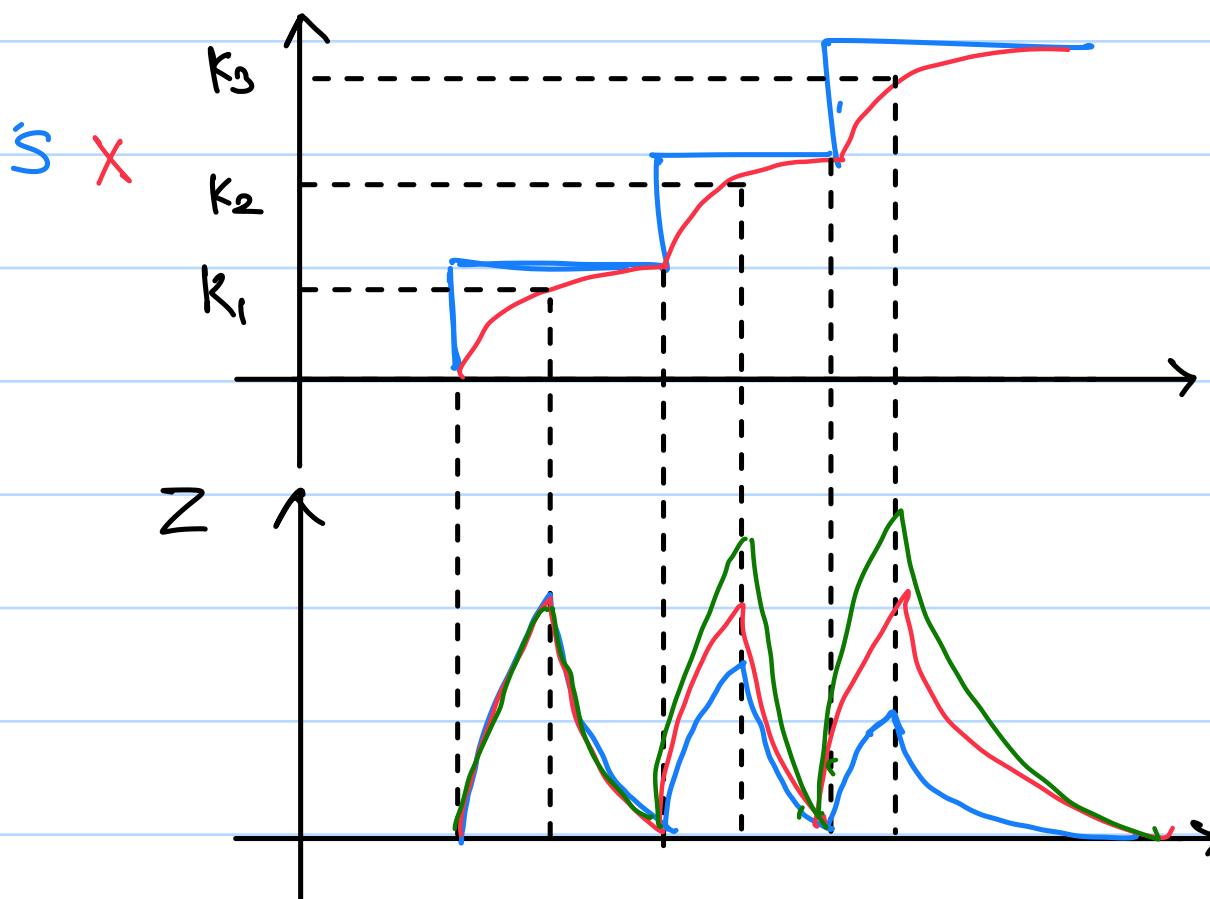
The height of the peak of R depends on the rate of production of R w.r.t X and also the value of K_{XR} , i.e. the time it takes for X to inhibit R.

For the peak to exist the effect of S on R must be lesser than the effect of X on R. Otherwise, the net fold change will still be creation, meaning Z will reach a non-zero steady state.

Rate Equation : $\frac{dX}{dt} = k_1 S - k_2 X$

$$\frac{dR}{dt} = k_3 S - k_4 X - k_5 R$$

Say, in the above mentioned incoherent FFL, S is actually an increasing stair-like function,



In such a stair-like increasing input, the peaks can either be

- 1) Decreasing - Adaptive Behavior
- 2) Constant - Fold Change deduction

Adaptive behavior is common when dealing with continuous sensory related stimuli.

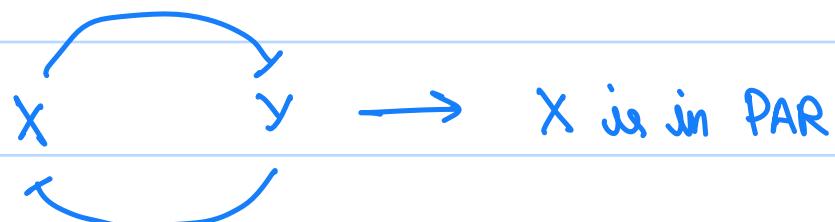
For fold change deduction, if $\frac{dx}{dt} = f(s, x)$ and $\frac{dR}{dt} = g(s, x, R)$

$$f(\lambda s, \lambda x) = f(s, x) \quad (\text{A change of } \lambda\text{-fold})$$

$$g(\lambda s, \lambda x, \lambda R) = g(s, x, R)$$

→ Phase - Plane Analysis :-

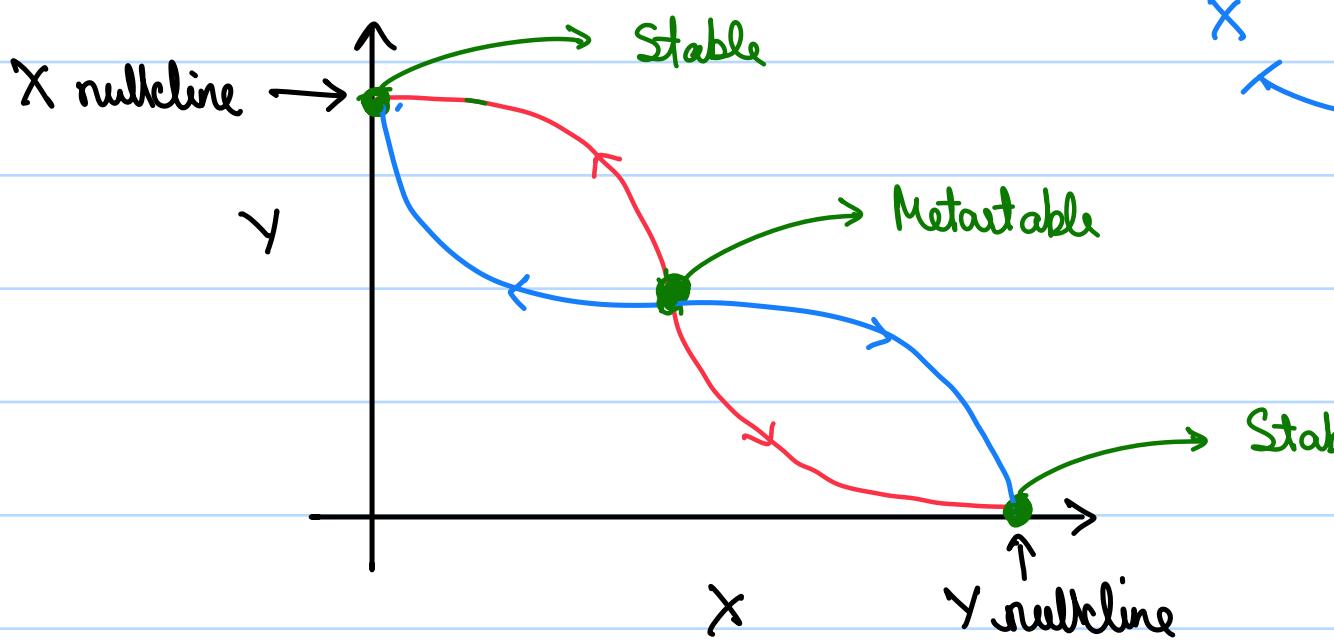
Say we have the circuit



$$\frac{dx}{dt} = \frac{\beta K_1^{n_1}}{K_1^{n_1} + y^{n_1}} - \alpha_x x \quad x \rightarrow y$$

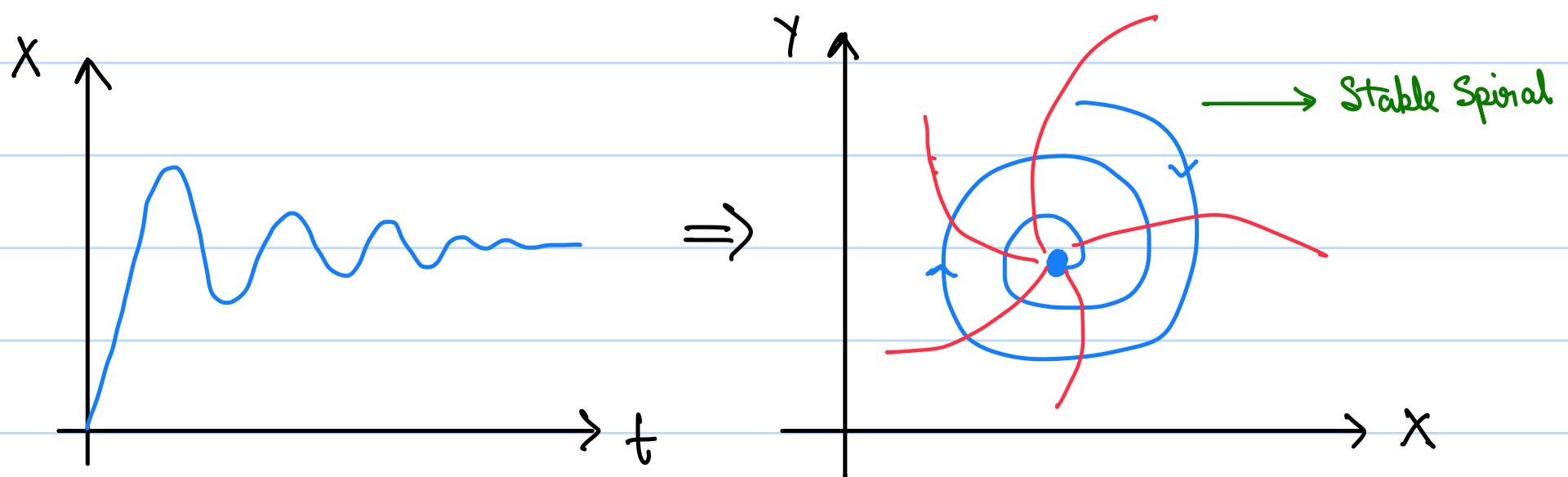
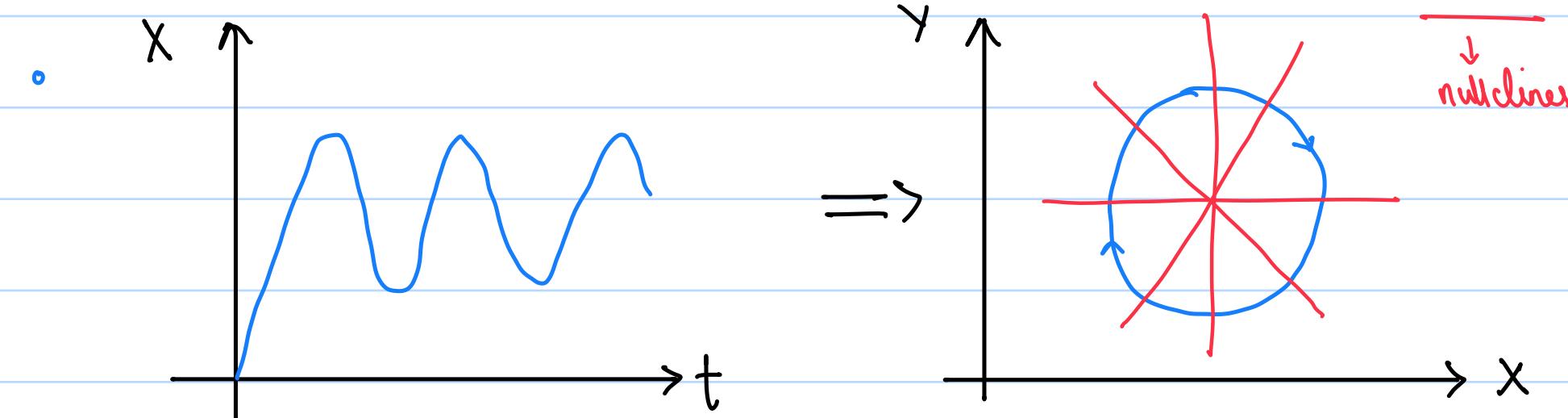
$$\frac{dy}{dt} = \frac{\beta K_2^{n_2}}{K_2^{n_2} + x^{n_2}} - \alpha_y y \quad y \rightarrow x$$

- The above dynamics is represented as.



- The above plot, showing the relation between the concentration of the different concentrations, is termed as phase-plane analysis.

- Nullclines - Curves of points when $\frac{dx}{dt} = 0$ or $\frac{dy}{dt} = 0$. → is \perp to the trajectory



To make an oscillatory circuit,



