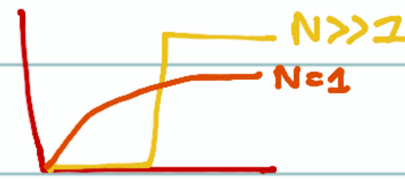
15th October, 2020

Class-5

Based on How oxygen binds haemoglobin to blood



$\frac{k_s x^n}{x^n + K^n}$ → Hill Equation

Graph could be hyperbolic/sigmoidal

Threshold to activate protein

Using $\theta(x > k)$ → Logical Approximation

Motif → Building Block [can't call it a system as they are simple having a recurrent pattern [repeats itself]]

"Subsystem"

Recurrent pattern

Example

n = 400 nodes. } Biological systems

m = 1000 edges

System Identification [Know the system like blueprint of car, aeroplane]

;

If we take bacteria, yeast [Network is identified]

Q. If we have system and check if we have recurrent motif, how do we prove?

Given network, for example 3 block components in a recurrent fashion, how to prove?

Answer: We take network of same size i.e. 400 nodes, 1000 edges for above example that can be a random network, then look for those recurrent components and check its statistical significance

☆ Read this online properly later 0:15:00

Example of random network

→ Erdos-Renyi Network:

"Scale-free Topology"

There are certain nodes densely connected signifying there are hubs, some organisational aspect is there.

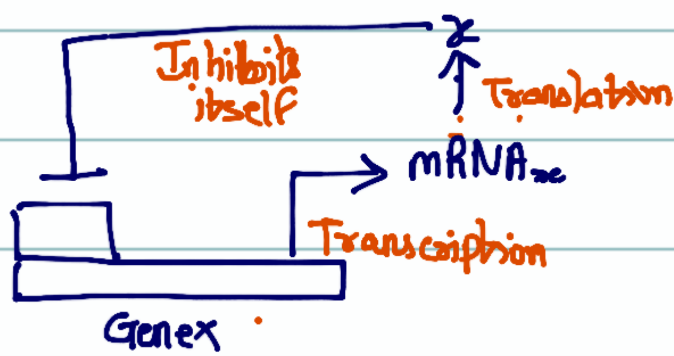
Motifs

"Negative Autoregulation"

Standard Nomenclature

$\dashv$ - Inhibition

$\rightarrow$ - Activation



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To write mathematical equation for auto regulated

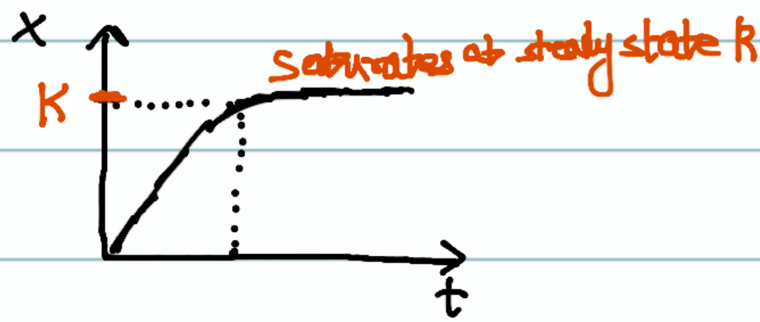
$$\frac{dX}{dt} = \frac{k_s K^n}{K^n + X^n} - k_d X$$ $X = $ Protein.

$$\frac{dx}{dt} = k_s \underbrace{\theta(x<k)} - k_d X$$

→ No inhibition when $x<k$ → 1

→ Inhibition only when $x>k$ — 0

K = { Inhibition Coefficient (or) Half Saturation Constant }



If we don't have auto-inhibition [$x<<k$], then x_{st} is simply given by

$$\boxed{x_{st} = \frac{k_s}{k_d}}$$

If $x << x_{st}$,

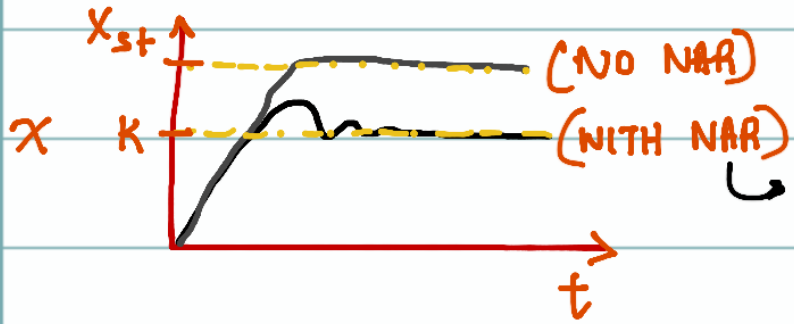
$$\frac{dx}{dt} = k_s \Rightarrow \boxed{x = k_s t + \text{Constant}}$$ → Linear initially

As time increases,

effect of degradation increases. As it approaches, threshold and settles due to damping

Will settle after " fluctuations

$$X = k_s t \Rightarrow x_{st} = \underset{(NAR)}{}$$

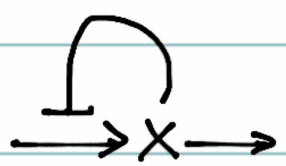


↳ Autoregulation like negative feedback

System won't reach actual steady state due to the feedback control which reduces the steady state value

Comparison

$$\xrightarrow[k_s]{\text{Sytheis}} X \xrightarrow[k_d]{\text{Degradation}}$$ [Simple System]



[NAR]

⊗ Design criteria: Have study state value to be same in both

For simple:

$$\frac{dx}{dt} = k_s - k_d X$$

$$x_{ss} = \frac{k_s}{k_d}$$

For NAR,

$$\frac{dx}{dt} =$$

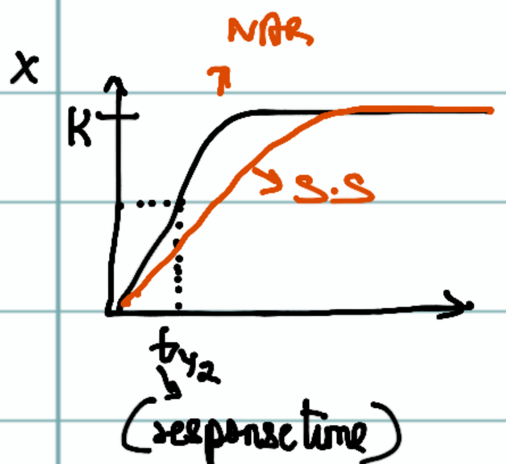
$$x_{ss} = k$$

We want to achieve

$$x_{ss(s.s)} = x_{ss(NAR)}$$

$$\boxed{\frac{k_s}{k_d} = k}$$

Possible when the autoregulation has



Simple system would take higher $t_{1/2}$ [response time] to reach same steady state

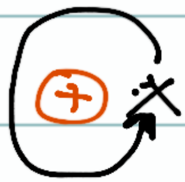
$$t_{1/2[\text{simple}]} = \frac{\log 2}{k_d}$$

To achieve same K; k_s should be very small for simple system.

But for autoregulation, for achieving K, k_s can be very large too. So, quickly reach steady state.

One of the other reasons to have NAR could be to use to respond very fast.

PAR [Positive AutoRegulation]



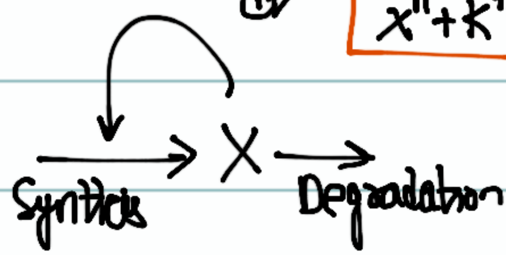
x activates itself

If X activates itself, promotes its

Mathematical Eq:

$$\frac{dx}{dt} = \boxed{\frac{k_s X^n}{X^n + K^n}} - k_d X$$

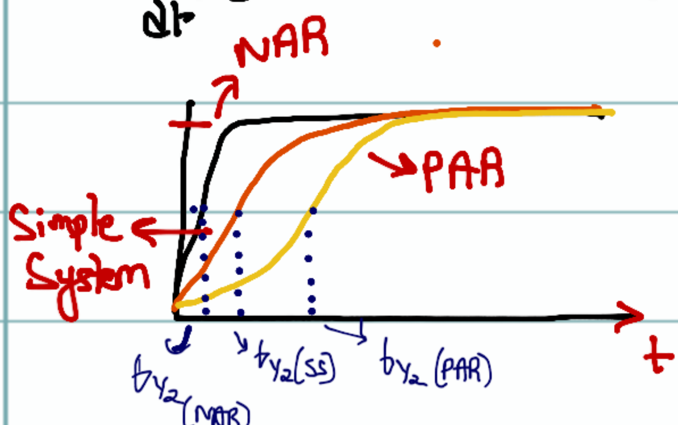
Very small till X reaches value of K



[Promotes its own degradation]

In this case, depends on how fast x accumulates

$$\frac{dx}{dt} = k_s \Theta(x > K) - k_d X$$



Response time increases for PAR

NAR is typically used in sensor systems..

Ex Eye, Nose .... "Sniffers"
NAR
& networks

- PAR is developmental processes with delays for long time like a commitment

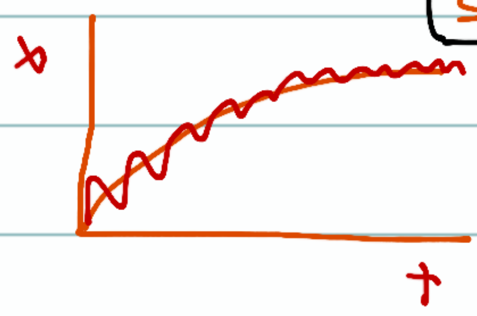
⇒ Response Time → Fast [NAR]
→ Delayed [PAR]

⇒ Steady State Response :

$$\boxed{\begin{array}{c} X_{st(ss)} = k_s / k_d \\ X_{st(NAR)} = K \end{array}}$$

→ Noisy / has fluctuations

→ Indicative of how well X can bind. Won't be very different with other cells. So, it is robust to fluctuations

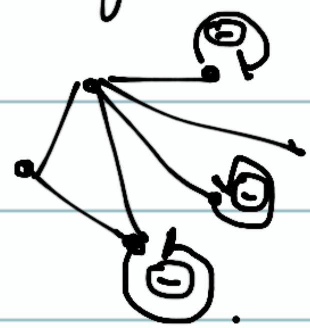


⇒ Output signal is noisy
& More noisy along steady state

⇒ Robustness :

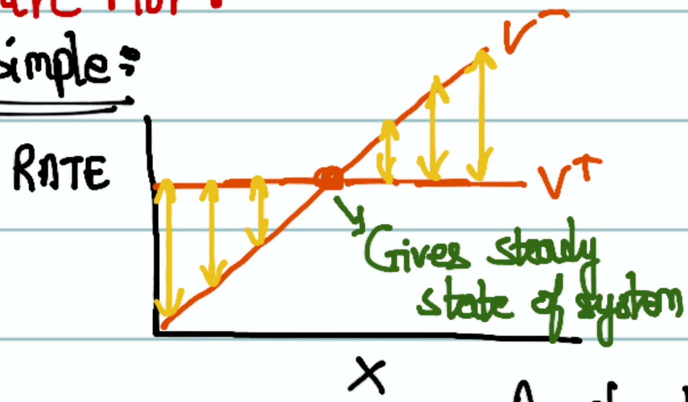
NAR has robustness as its X_{ss} is resistant to fluctuations

Example of a network



Rate Plot:

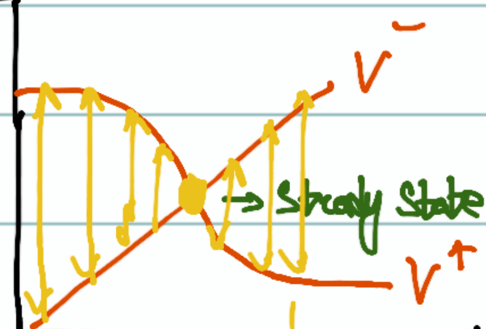
Simple:



$$\frac{dx}{dt} = \underbrace{k_s}_{V^+} - \underbrace{k_d X}_{V^-}$$

Acceleration decreases towards steady state

NAR:



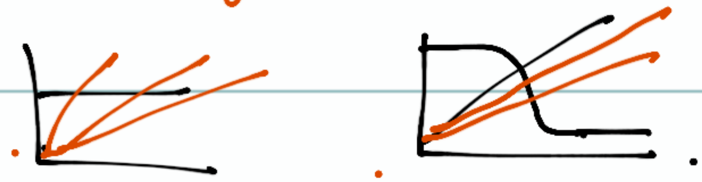
$$\frac{dx}{dt} = \underbrace{\frac{k_s X^n}{X^n + K^n}}_{V^+} - \underbrace{k_d X}_{V^-}$$

Can be hyperbolic or sigmoidal

Initially we see acceleration is huge

If k_d is fluctuating, slope of V^- will keep changing accordingly resulting in change of steady state

Comparison of SS, NAR in terms of robustness with plot



Steady state values change very dramatically for LAR.
Whereas, the simple system has a lot of fluctuations
signifying not robustness of NAR but not there in SS.

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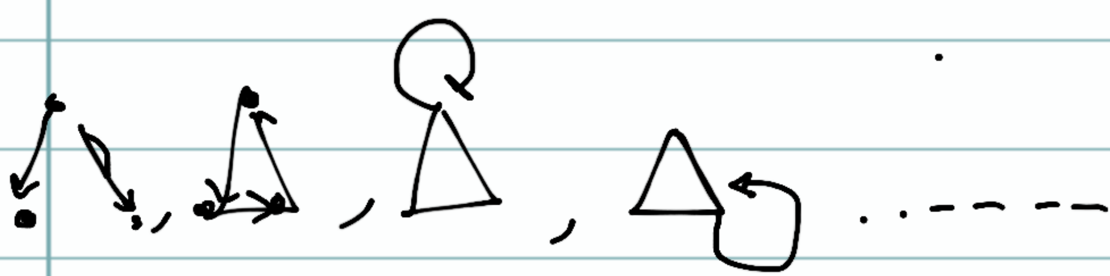
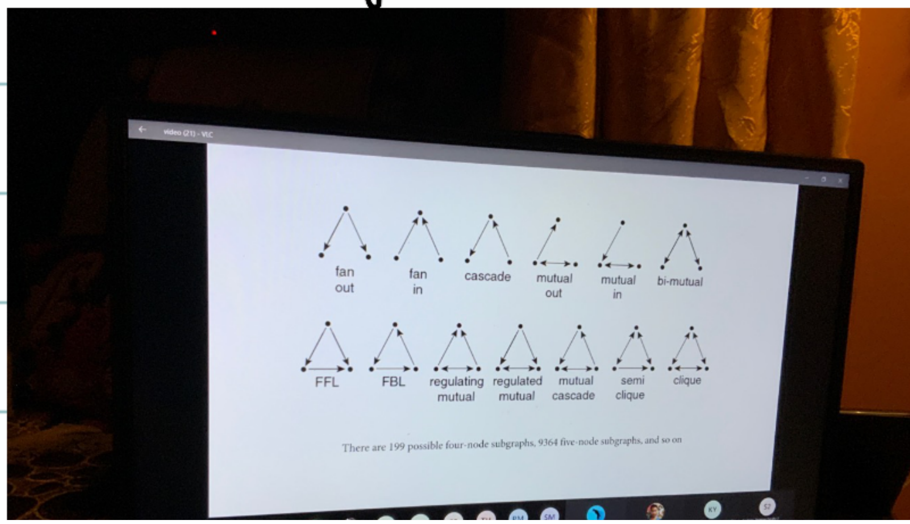
3 Component MOTIF | Subsystem



There are 199 - 4 node system



Feedforward Systems :

↳ 'Feedforward loop'

If there are 3 nodes, $\begin{tikzcd} X \arrow[r, "+"'] \arrow[rr, bend left, "+"] & Y \arrow[r] & Z \end{tikzcd}$, then X can activate Z directly and indirectly. Acts like a AND/OR method for activating Z.