

SYSTEMS

BIOLOGY

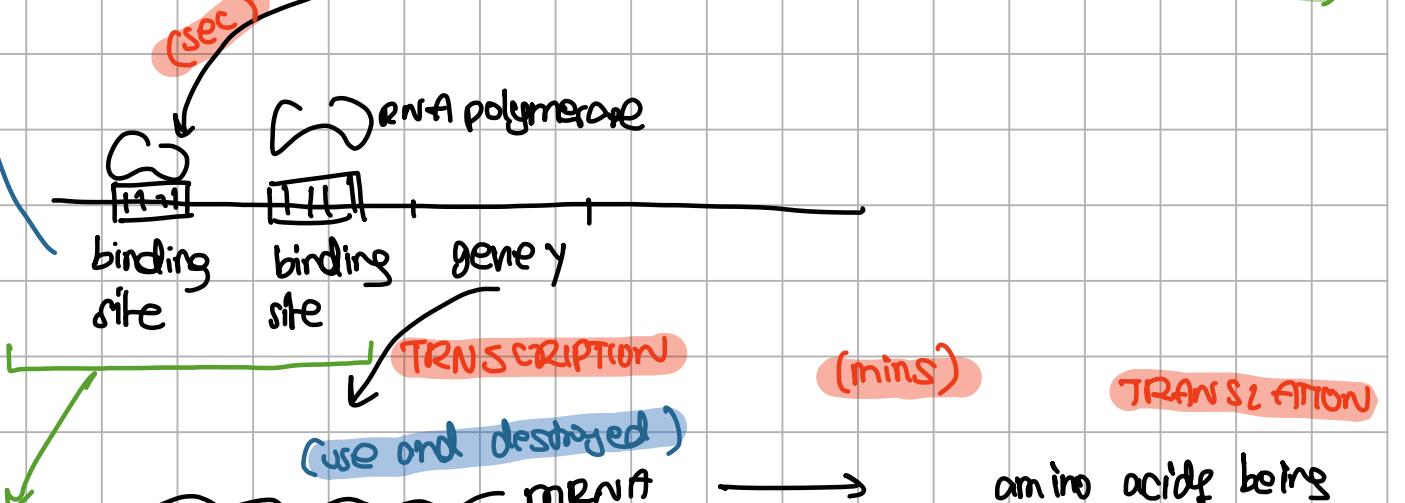
Translation-Transcription

this can be > 1 ; like x_1 and x_2 but not y_1 or y_2 and $2 > 30\text{min}$
then RNAP go! :D

Transcription factor : TF : special sets of proteins

(TF) say X :

$X \xrightleftharpoons[S_x]{\sim} X^*$ (inactive/active switch) (+S) (shape change really)



(short copy of gene)

(mRNA or less))

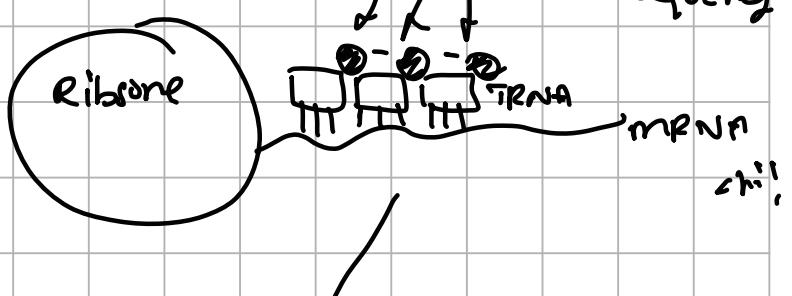
this part
is called
the promoter

of the gene which regulates

when do express gene - y

X^* helps RNAP bind and hence

express gene - y

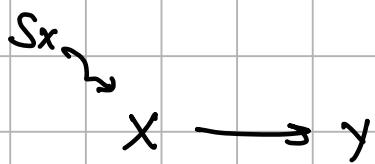


3D protein 1 (y)

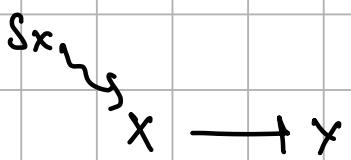
for many notable Ys

(hours)

Symbolically -



X can ↑ Y production : activation

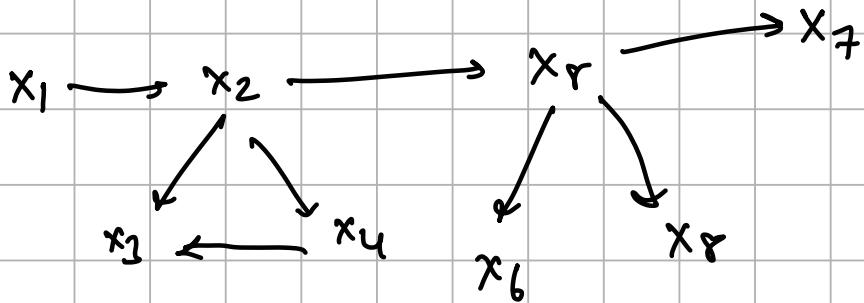


X can ↓ (they restrict : repressors
RNA polymerase)

Gene Regulation Network

Graph with all the regulations

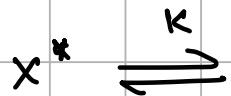
$A \rightarrow B$ means A regulates B



TFs are the only nodes with out-going arrows

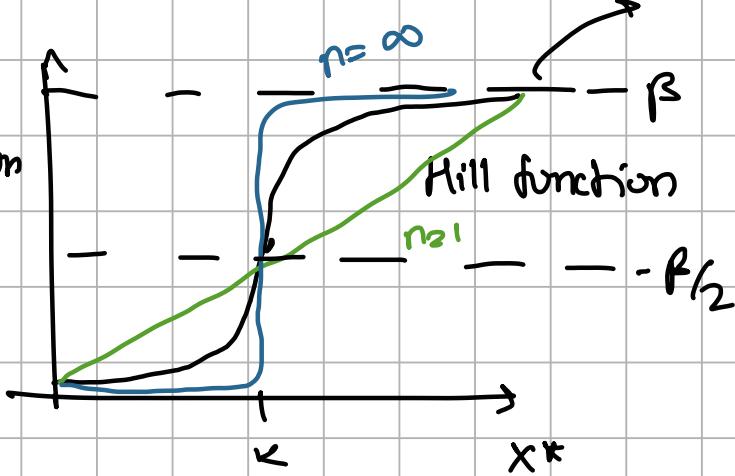
the arrows can also have weights

Activator



Binded to regulatory binding site

rate of
Y production



if there is
~ x^* it
is bound
to bind
dissociate
so there
is a
saturation
point.

Remember x^*

changes the rate of
production of Y not
for 50% activity

Y

$$\frac{dy}{dt} = \frac{\beta(x^*)^n}{k^n + (x^*)^n}$$

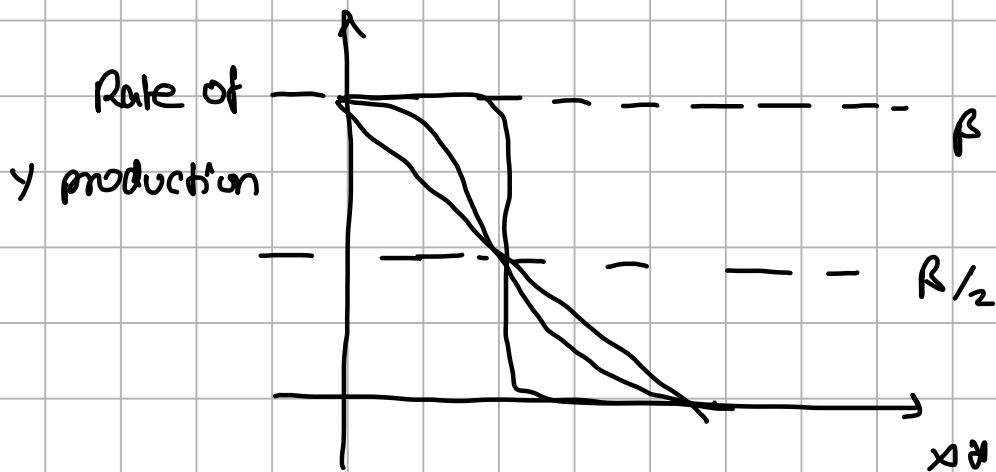
| β is not maxⁿ
n is how steep curve is

Practically n: 1-4 in real biological circuits.

At n=∞ it a binary function! $x^* > k$ then β

$x^* < k$ then 0

Repressors



$$\frac{dy}{dt} = \frac{\beta^{k^n}}{(x^*)^n + k^n}$$

(if β - previous y)

Equation for the dynamics of a single arrow-

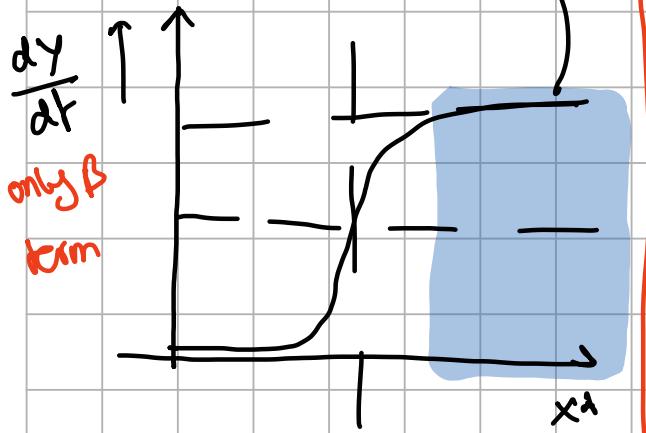
if this is realistic $\because x \rightarrow x^+$ is in ps so I can saturate x^* v. quickly and do my f analysis at $x^* = \beta$

$$\frac{dy}{dt} = \boxed{\beta} - \alpha y$$

only this part

in this region

if β



1. proteasomes convert $y \rightarrow$ amino acids (α_{deg})

2. dilution by cell growth i.e.

in pro-phase the protein fails to duplicate so in a way it undives right (α_{dil})

At steady state

$$\frac{dy}{dt} = 0$$

$$0 = \beta - \alpha x_s \Rightarrow x_s = \frac{\beta}{\alpha}$$

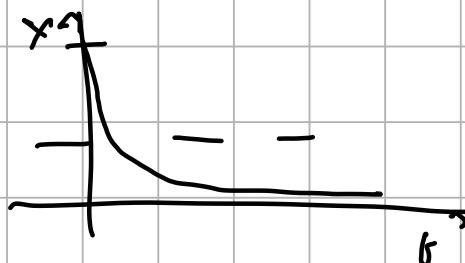
Response time

v. possible if terms only
μs

- Say at y_t $\beta \rightarrow 0$ suddenly \rightarrow I cut the sugar supply

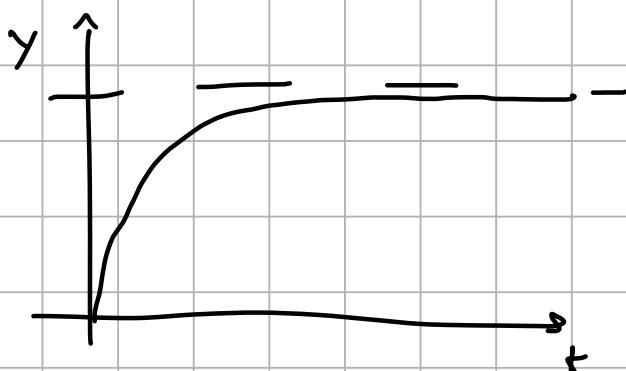
$$\frac{dy}{dt} = -\alpha y ; y = y_s t e^{-\alpha t}$$

$$t_{y_2} = \frac{\ln 2}{\alpha}$$



- Say suddenly you add sugar now $\beta \rightarrow \beta'$

$$\frac{dy}{dt} = \beta - \alpha y \quad | \quad y = y_s t (1 - e^{-\alpha t})$$



$$t_{y_2} = \frac{\ln 2}{\alpha}$$

∴ Therefore the response time of both of these cases depends only on α ; which is the natural undiluting rate of the protein thru proteasomes or dilution

$\sqrt{\alpha}$ of which
is apparently is ≈ 0 (the formed proteins are really stable)

(they can take lot more time than stable ones)

so $\frac{\ln 2}{\alpha}$ is $\frac{\ln 2}{\alpha + \alpha_{dil}} = \frac{\ln 2}{\alpha_{dil}} = 1 \text{ cell generation}$
 $(Y(t) \rightarrow Y(t)/_2)$

($\text{---} \rightarrow \text{---}$)

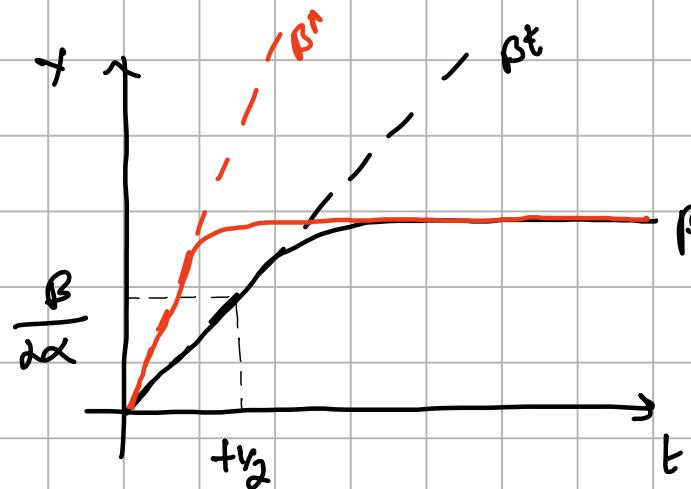
which is really slow!

so if a cell wants to make Y only if children
grandchildren will end up seeing it. It's really slow!

Motifs

Complex networks are made of simpler circuits - network motifs

It Short review of last time -



crudely

$$\beta \cdot t_{1/2} = \frac{\beta}{2\alpha} \Rightarrow t_{1/2} = \frac{1}{2\alpha}$$

$\sim \frac{\ln 2}{\alpha}$

$$t_{1/2} = \frac{\ln 2}{\alpha}$$

- response time depends only on α

If you $\uparrow \alpha$;

response time \downarrow bt

steady state would also

drop, so you would end up with few y bt quickly.

If you are breaking

a lot (α^1) you must

also be making a lot

so βt only then you

would end up with reasonable

quantities of y .

$$\frac{dy}{dt} = \beta - \alpha y ;$$

start 1α , y is too small

$$\text{so } \frac{dx}{dt} = \beta \text{ then } \frac{dy}{dt} = \beta - \alpha y$$

steady state reached

So why not make break quickly - quickly.

It costs a lot of more resources now per unit time.

Needlessly making-breaking so many times a sec!

∴ cells instead make stable proteins ↓ breaking ↑ response time

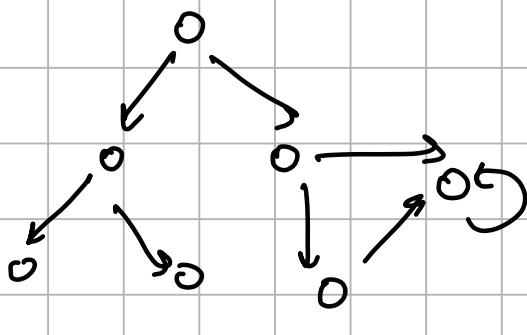
↑ steady state

Nature has discovered a neat trick

that can reach a steady-state at desired response time

without needing unstable, quickly breaking proteins

The magic



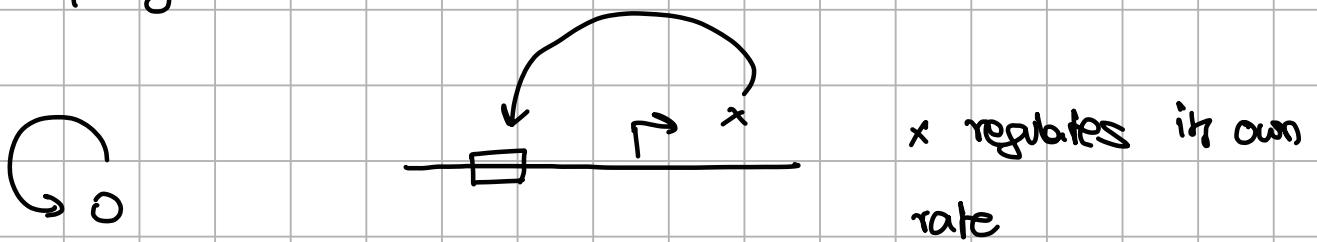
We shall then
look for patterns
(sub-graphs) that
occur often

However correlation \Rightarrow Causation

so we compare it to a sample of random
graphs with same properties

That subgraph is then called network motif.

self-regulation



E-coli

Has $N = 400$ genes

(one mRNA can hold more than 1 gene)

$E = 100$ arrows

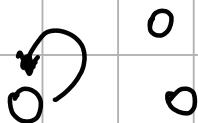
$N\text{-self} = 40$

- for a random network let take and topology with

$$N = 400 \quad E = 100$$

for each node, the probability that it loops to itself is $\frac{1}{N}$

(given every connection is equally-likely)



$$P(\text{self}) = \frac{1}{N} \quad N = 5 \text{ nodes}$$

How many self-edges in random network?

X be the number of self-edges

$$X = X_1 + X_2 + X_3 + \dots + X_{400} ; \text{ where } X_i = 1$$

if self-edge

$X_i = 0$

if not

$$E(X) = \sum E(X_i)$$

$$E(X_i) = \sum x_i P_{X_i}(x) = 1 \times P_{X_i}(1) + 0 \times P_{X_i}(0)$$

$$= 1 \times P_{X_i}(1) = 1 \times P(\text{Edge is a self edge})$$

$$= 1 \times \frac{1}{N} = 1 \times \frac{1}{400}$$

(every node is equally

$$\therefore E(X) = \sum E(X_i)$$

likely so it has 400 options)

$$= \frac{400}{400} = 1.25$$

so in a random graph the number is 1.25

but in our σ -coli it's 40 (look at the difference!)

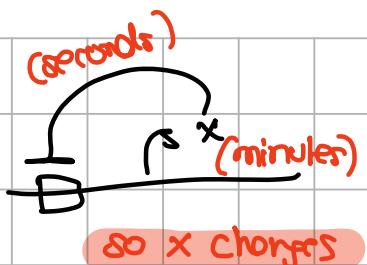
It's as if it's here on purpose

and not by chance)

Back to E-Coli

$34/40$ are NAR: negative auto regulation





x binds to the regulatory binding site

and decreases its production rate.

slowly compared to its binding rate otherwise there would be oscillations

If you could ignore how long it takes for

x to bind? that need not be modelled as a sep diff. eq

Re-wiring happens with mutations, say the binding site

has a letter change then $x \rightarrow X$ stops. If this becomes

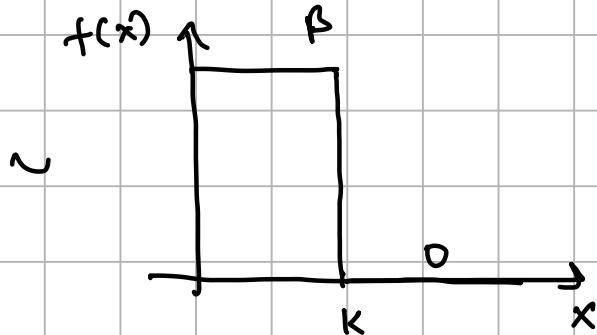
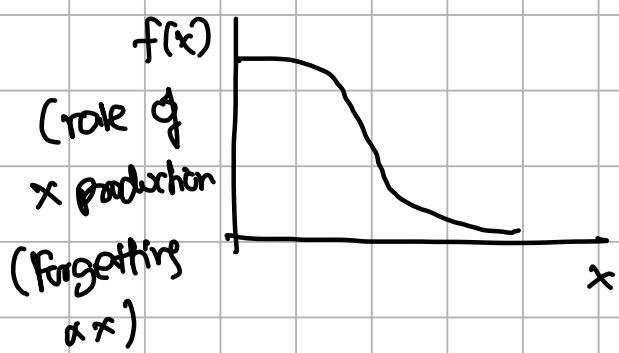
more favourable these organisms will evolve.

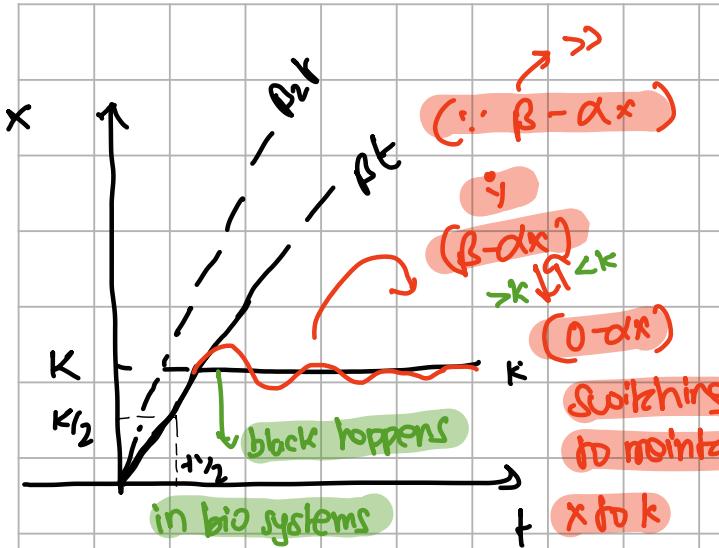
NAR : Negative Auto Regulation

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

(proteasome + dil)

$f(x)$ should be a decreasing function of x 'cos inhibition





But because of the time-scales
it makes sense to not have oscillations!
really!

k : equilibrium binding fixed
constant based on topology
of the site - it can't be changed.

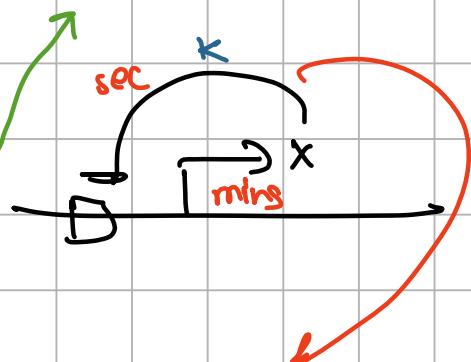
(Sir claims k to be "amount of
 x for 50% binding")

Obv. this is a fixed no.

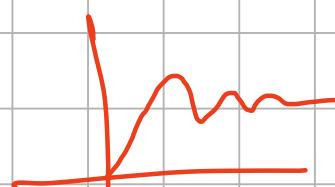
∴ Steady state is fixed

$$\sim \beta + \frac{1}{\alpha} \approx \frac{k}{2}$$

$\Rightarrow t_{1/2} \sim \frac{k}{2\beta}$ depends on β
and not α



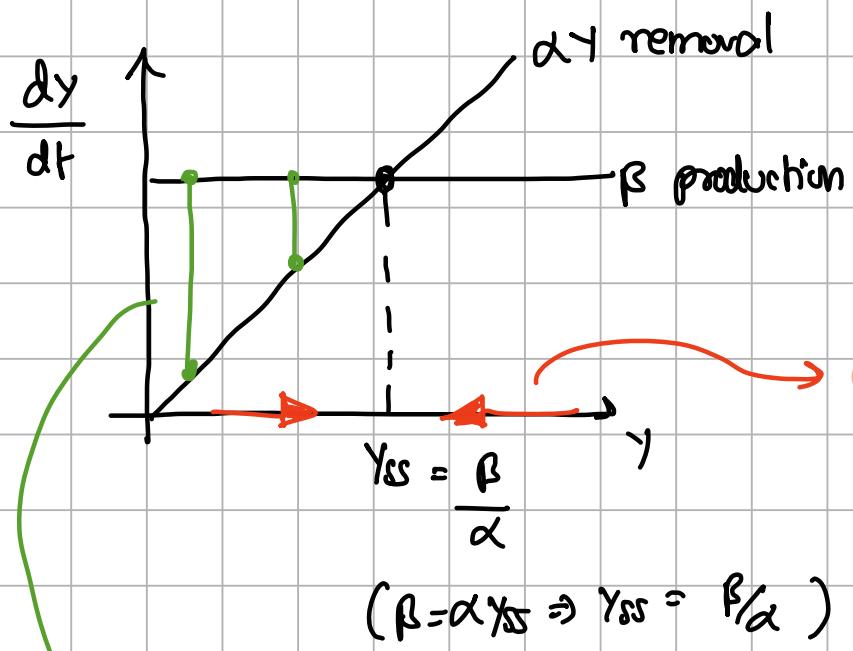
It takes 1 min for x
to be made say it took
another min for x to bind
You will have $2x$ and then
it would respond to old ix
conc. say $2x$ is shutoff time
but $2x$ is not detected yet
so $3x$ happens and $2x$
is now detected so on and on



But if
conc. levels
can make
a change in
seconds! Then
instantaneous

$\therefore \beta \uparrow$ can be done without affecting steady state

Another technique - rate analysis



Simple regulation

speed

$$\frac{dy}{dt} = \beta - \alpha y$$

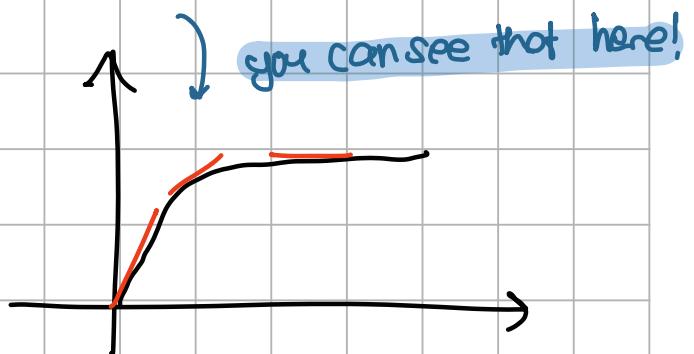
depending on what y you start of with
the graph will approach
from \rightarrow or \leftarrow

towards the steady state

The distance (difference)

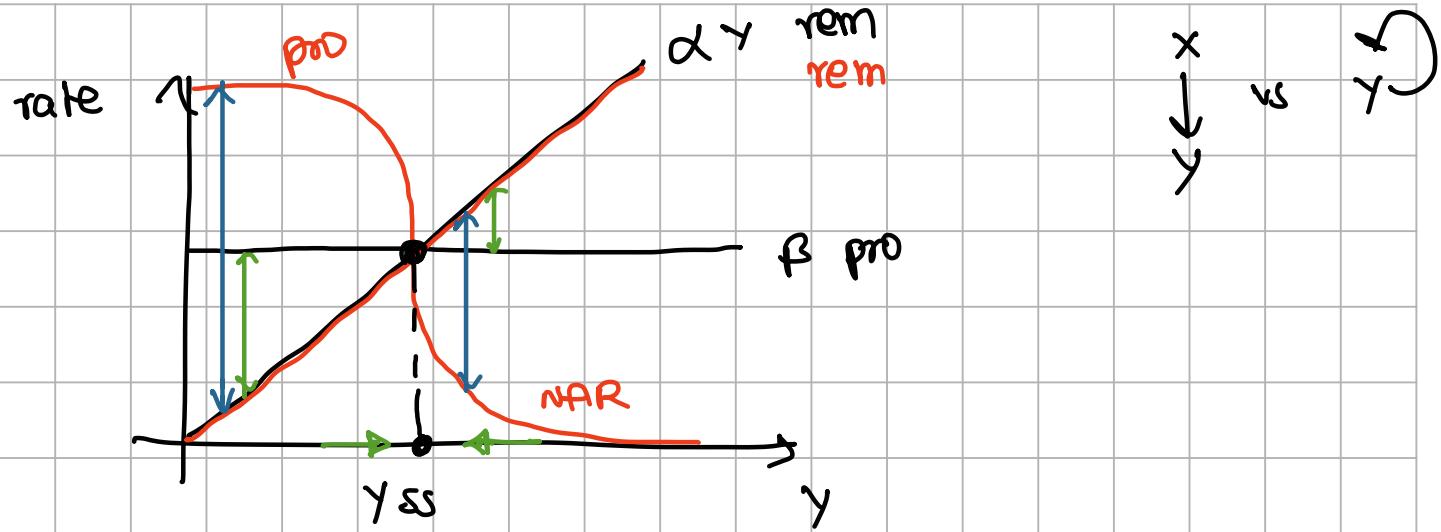
between those 2 lines is the speed (rate)

of the reaction



you can see that here!

If whenever you do a comparison, it's good to do it with same metrics, that's why for our NAR, let steady state and response time remain the same.



Speed of NAR > **Speed of simple regulation**

Always!

\therefore NAR is actually faster than simple regulations!

Noise regulation

NAR makes x_{ss} robust to natural variations in production, cell-generation.

In biology noise can be quite large - I didn't really understand this part but he said the numbers are so small so noise% is quite high

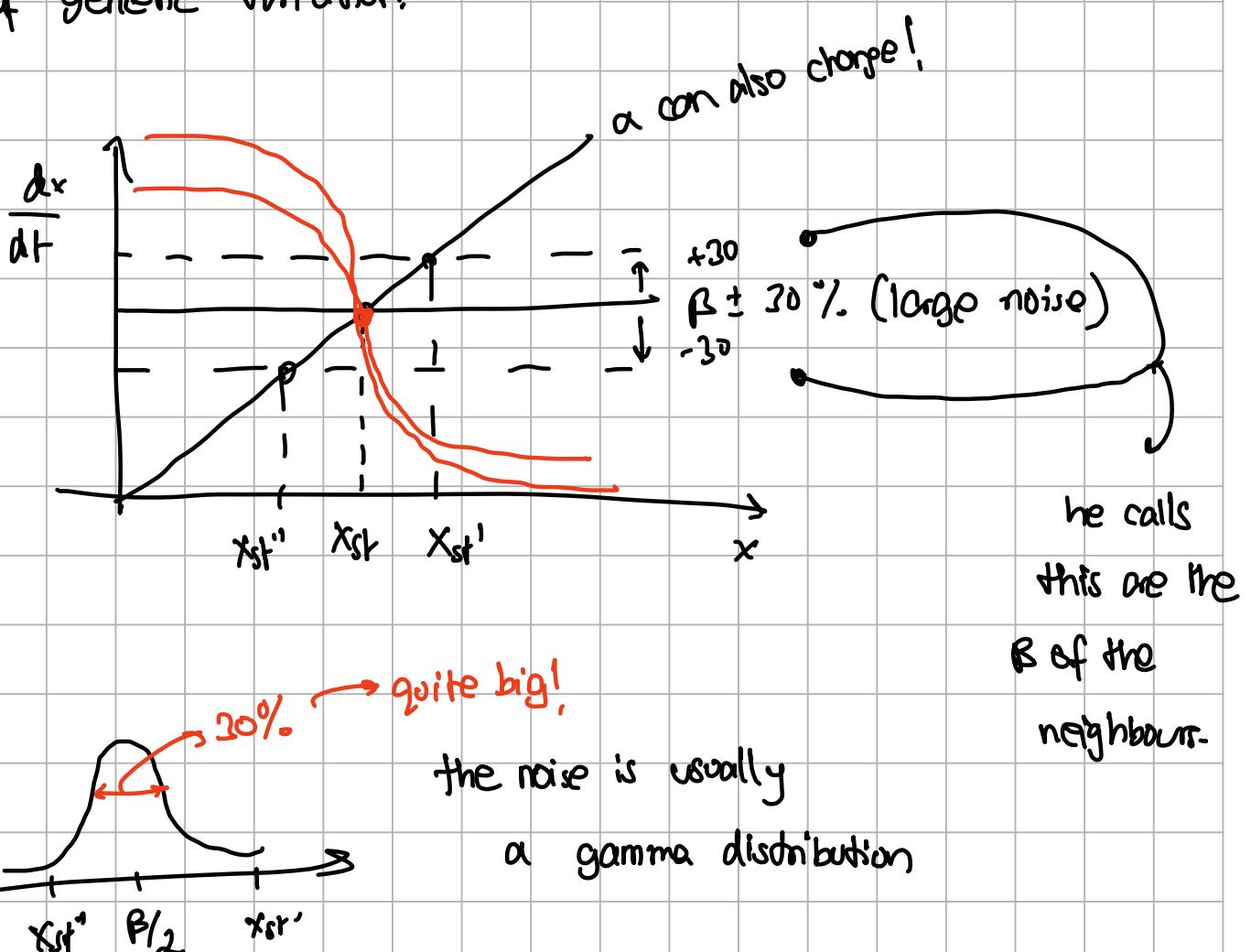
10 ribosomes in cell 1 or 6 ribosomes in cell 2

at a given time
the variation is large?

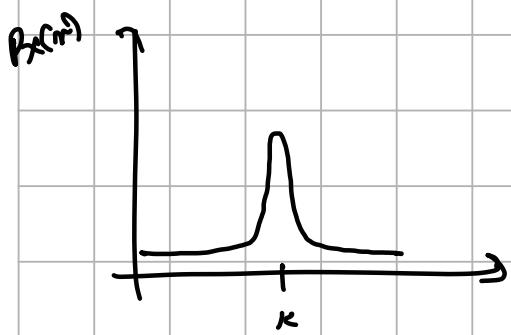
NOT SURE

But what I actually understood is that even tho Nasu is quite high precision is very much necessary; say 100 cells do 100 cells grow; if this no. is off I will either explode or collapse exponentially. - robustness.

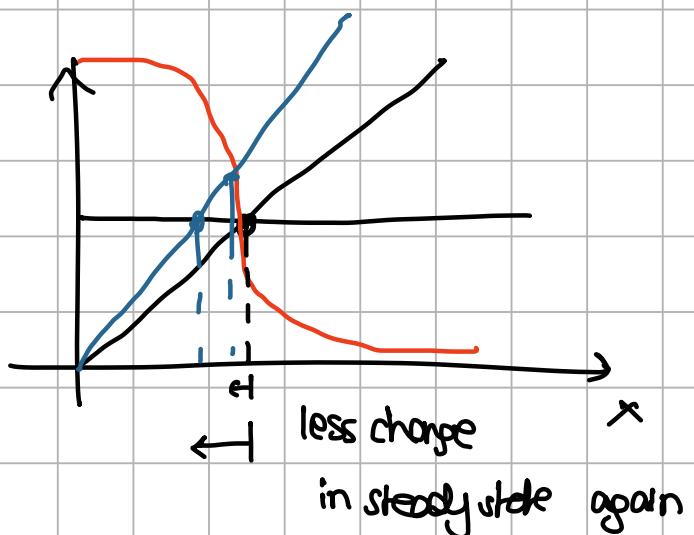
At the same time noise is also amplified! Like in the case of genetic variation.



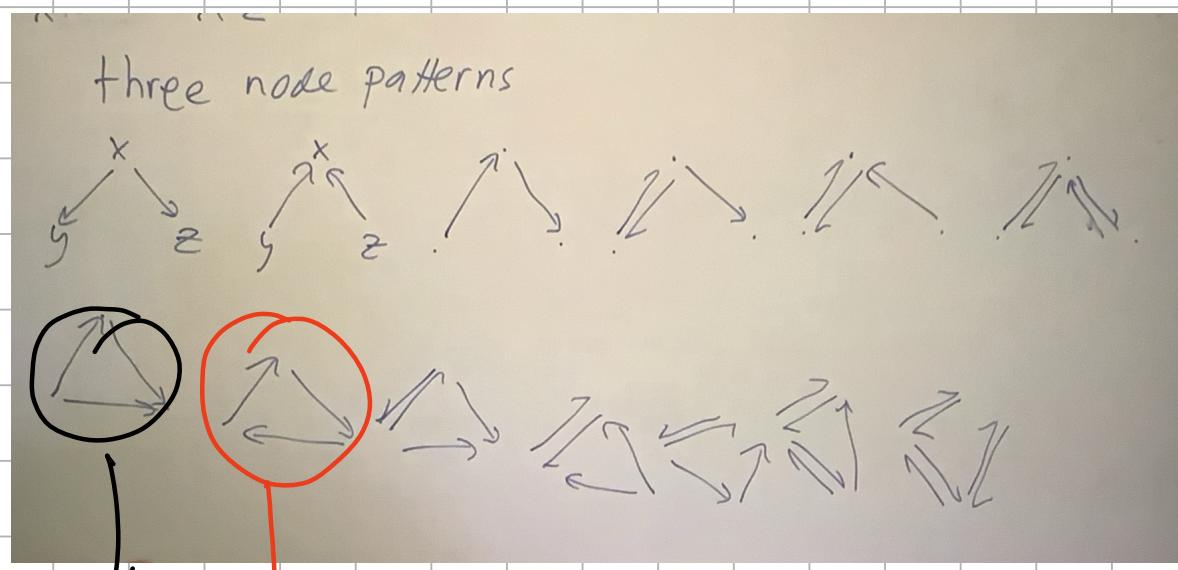
for NAR; K is hard-wired it would change only if there were a mutation (I think). The sst is fixed! ~ very small noise,



Even for the α shift



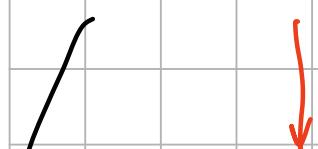
3-node patterns



occurs 42 times in real network

motif

while in a random network it occurs 2 times



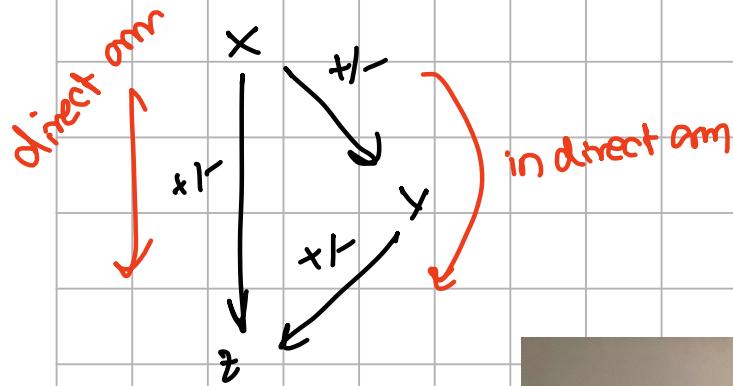
occurs 0 times in real network

while in a random network it occurs some times

anti-motif

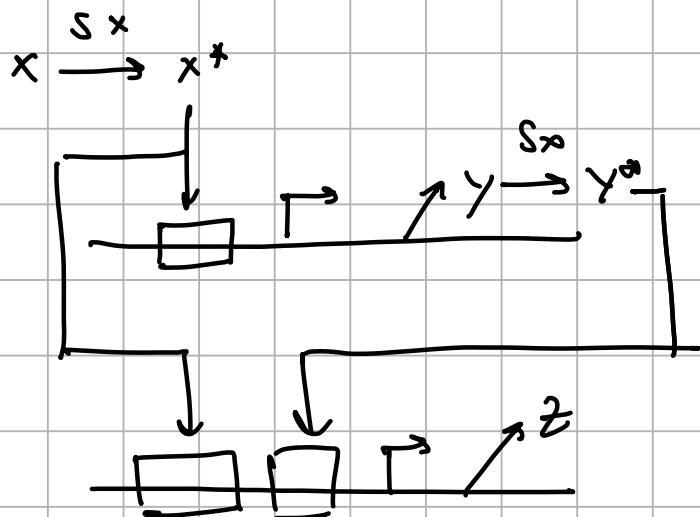
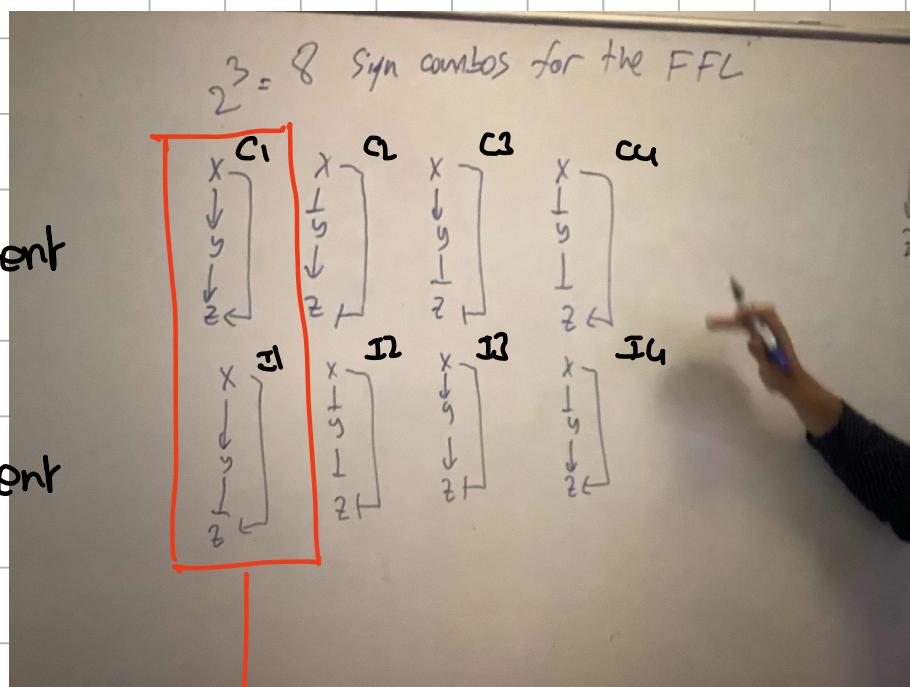
I called the feed-forward loop

$\text{FF} \uparrow$ That motif is called the feed-forward loop

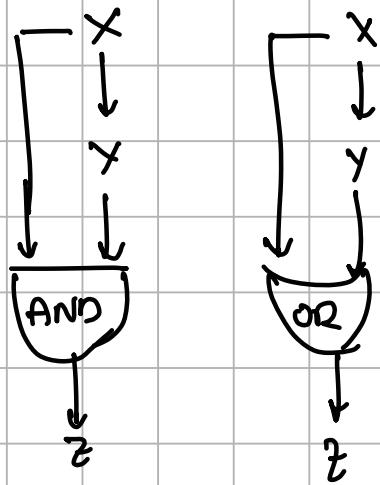


when both : coherent
arm's do same
things

when both in-coherent
arm's do diff.
things.



- It could be
- X AND Y
- X OR Y



Assymetric delays!

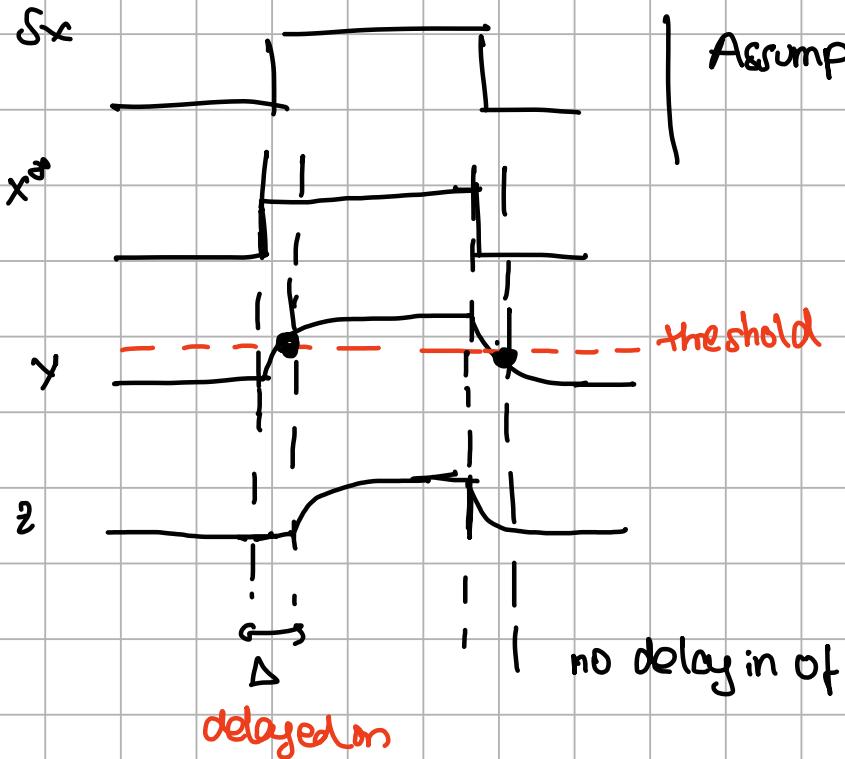
(Sign-sensitive delays)

~ Some terminologies before that,

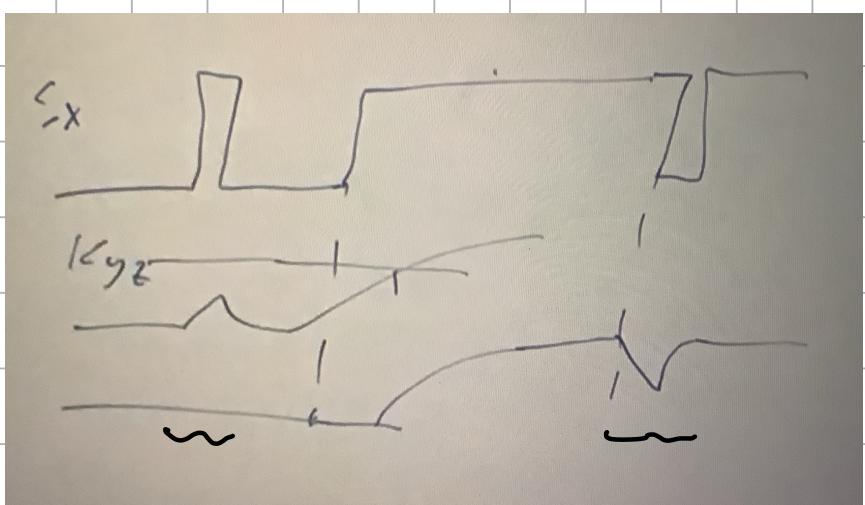
ON-STEP: → activation

OFF-STEP: → inactivation

AND -



Also note: z does

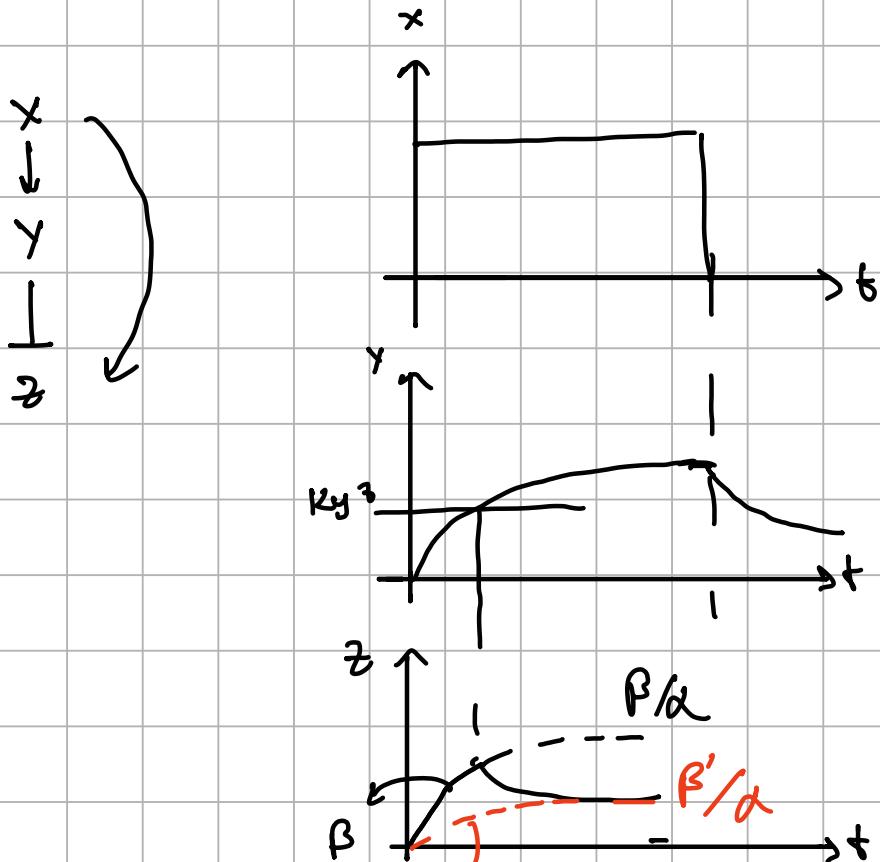


not respond to
small peaks but
responds to small
notches.

it filters out brief on

fluctuations but not off

Incoherent Feed-forward loop -



3 ways to speed up!

1. $\uparrow \alpha \uparrow \beta$

2. NAR: But works only
for TF's (only to make
TFs)

3. IFFC which works
in expressing any gene

We get
a pulse

if it were a simple
regulation, it would just be

β'/α , slow rise

so what nature does it
uses fast β and then

sharp breaks to reach β'
(desired.)

Development Gene Regulation networks (PAR)

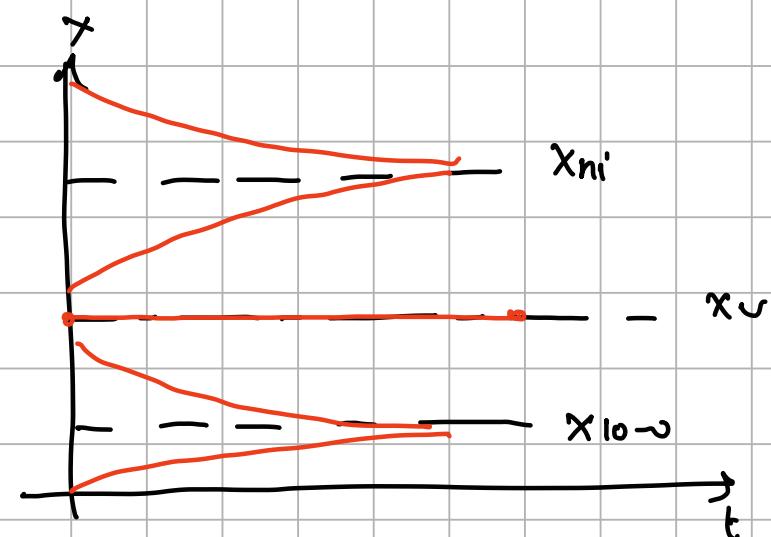
(Can provide memory)

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

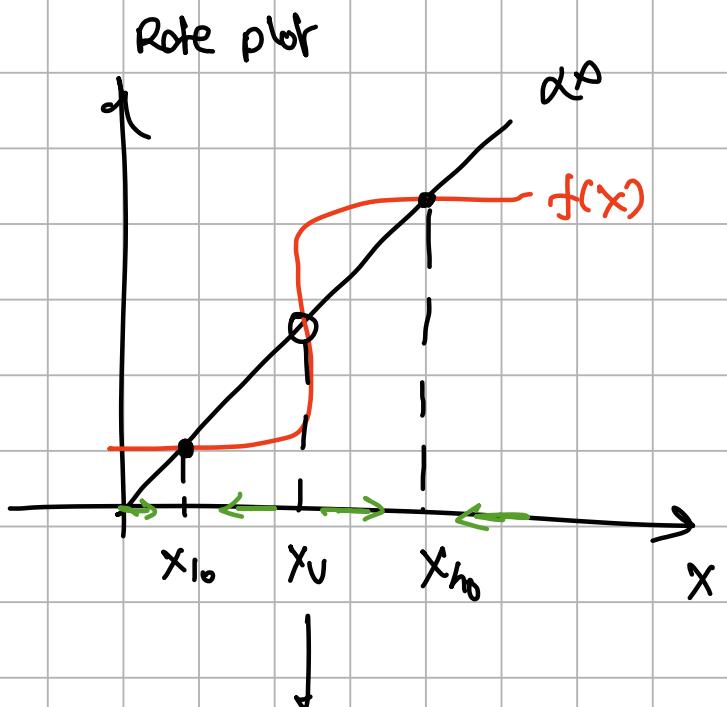
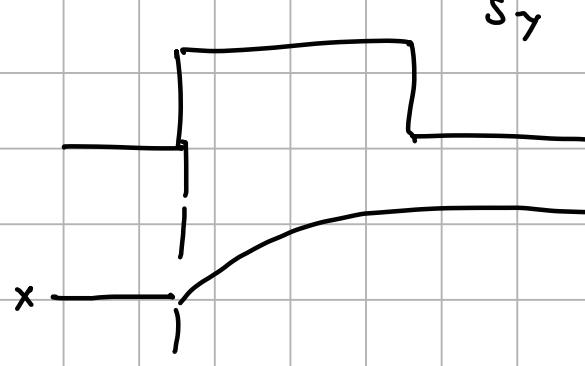
- one circuit has

2 stable fixed points

bi-stable

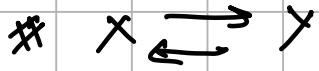


$y \rightarrow x^2$



unstable (only at that point stable for small push will yank it somewhere else)

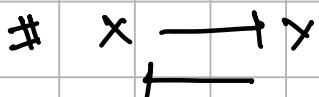
stays high
even if y stops fueling it.



Has two stable fixed points

- $X_{\text{high}}, Y_{\text{high}}$

- $X_{\text{low}}, Y_{\text{low}}$



- $X_{\text{high}}, Y_{\text{low}}$

- $X_{\text{low}}, Y_{\text{high}}$

A mathematical tool for analysing such graphs

Nullclines : (Systems with 2 variables)

(Rate analysis is good enough for 1)

Consider  (Toggle switch)

$$\frac{dx}{dt} = f_1(y) - \alpha x$$

| f_1 is a decreasing function with $y \uparrow$

$$\frac{dy}{dt} = f_2(x) - \alpha y$$

| f_2 is a decreasing function with $x \uparrow$

Solⁿ for

$$\frac{dx}{dt} = 0 \quad \text{nullcline 1}$$

$$\frac{dy}{dt} = 0 \quad \text{nullcline 2}$$

$$\frac{dy}{dt} = 0 = f_2(x) - \alpha y \Rightarrow \alpha y = f_2(x)$$

$$\Rightarrow y = \frac{f_2(x)}{\alpha}$$



Says: $y = f_2(x) \times \frac{1}{\alpha}$

i.e. a function
of x !

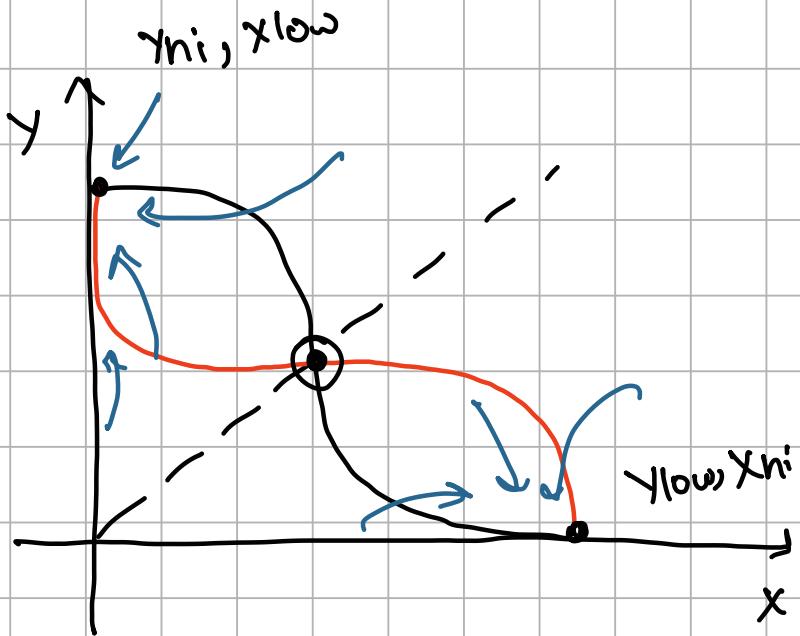
(the same sigmoidal
shape, just scaled)

$$\frac{dx}{dt} = 0 = f_1(y) - \alpha x \Rightarrow \alpha x = f_1(y)$$

$$\Rightarrow x = \frac{f_1(y)}{\alpha}$$



Now on one graph -



The intersection of

$$\frac{dx}{dt} = 0, \frac{dy}{dt} = 0$$

are points (x, y)

on settle into

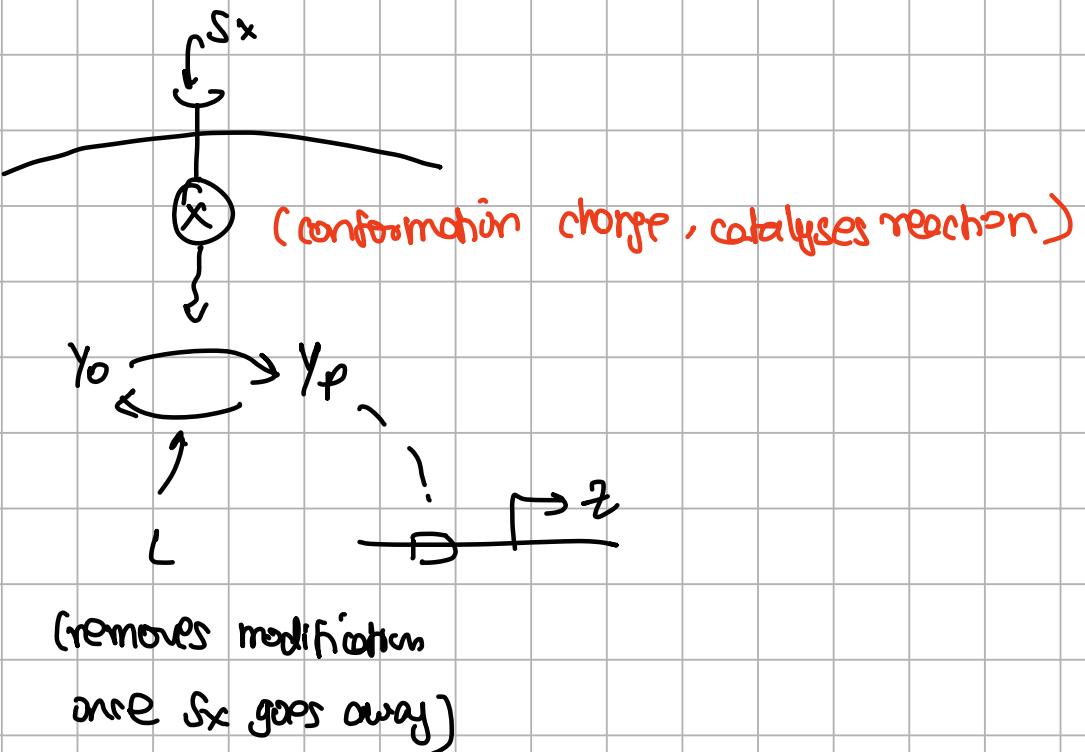
You need to do some more mathematical analysis to
be able to draw these blue lines but this is what happens

** Many others

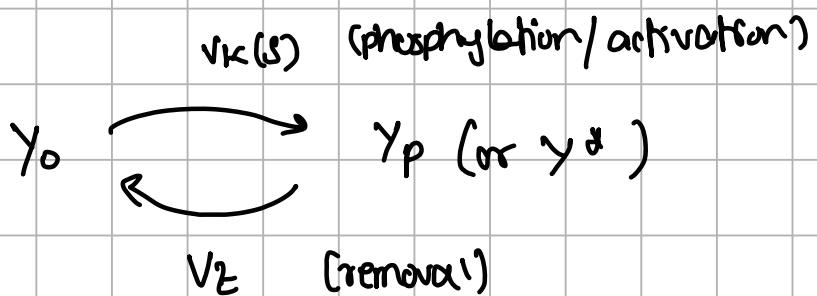
$$G_x \rightleftharpoons y?$$

PAL come upon each of the nodes to further
ensure a locked in state

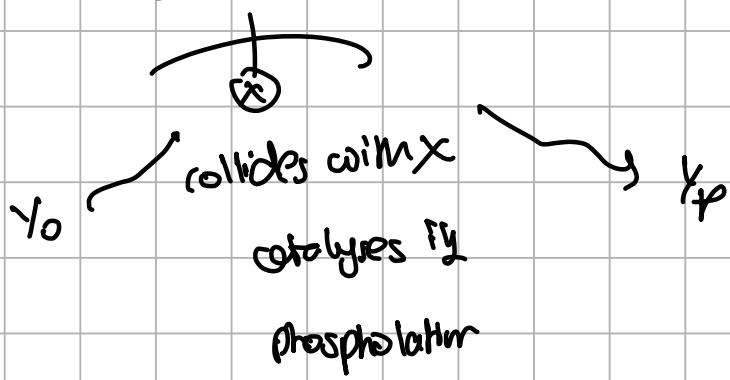
Signal transduction



Equation :



$$\frac{dY_p}{dt} = \text{basically collisions}$$



(mass action)

$$= (Y_0 X) V_{k(s)} - (Y_p \beta) V_2$$

of reactant)

(v₂ collision)

if they collide
 this is the prob.
 that it is successful

$$v_{k(S)} \rightarrow \frac{\text{activity}}{\text{receptor (which is } S\text{)}} \quad \begin{pmatrix} \text{rate of phosphorylation} \\ \text{per receptor} \end{pmatrix}$$

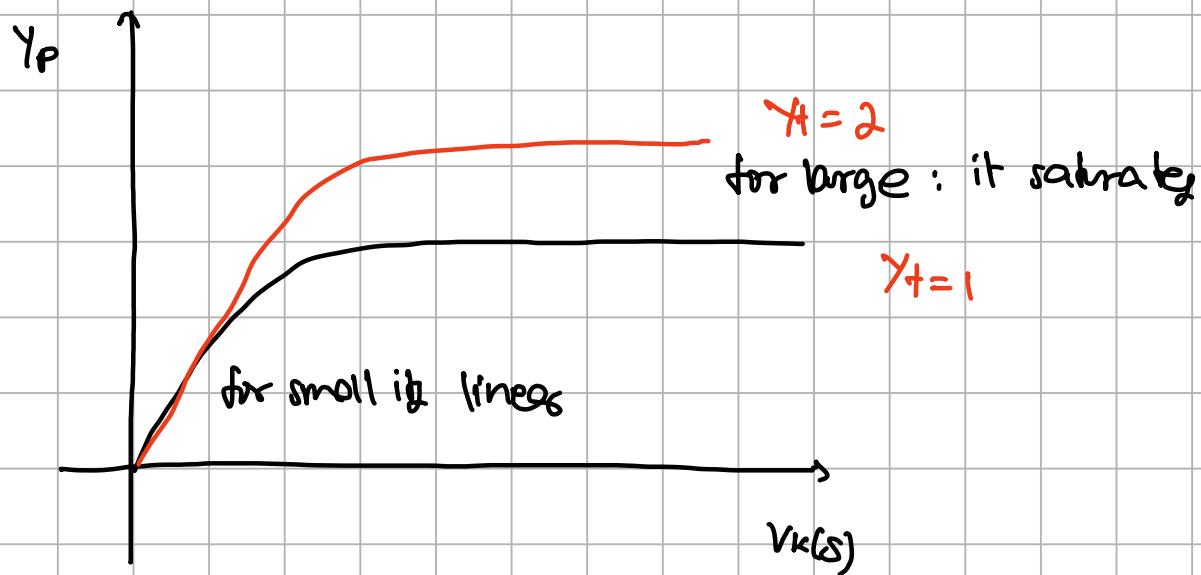
V_t → rate of dephosphorylation per receptor

$$\text{Also, } Y_0 + Y_P = Y_T \quad (\text{total})$$

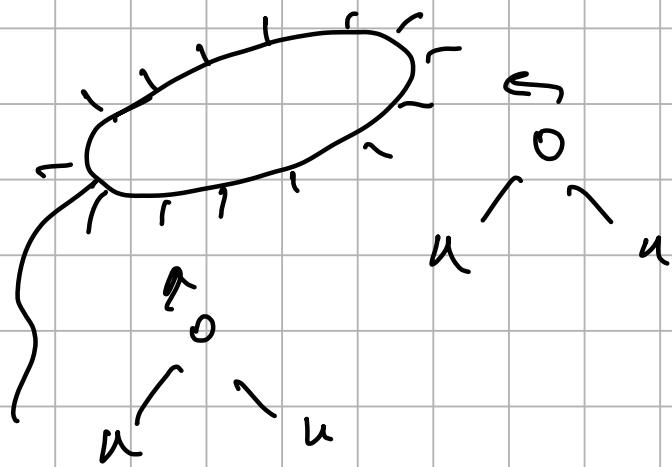
$$\frac{dy_p}{dr} = (\gamma_T - \gamma_p) \times v_k(s) - (\gamma_p z) v_z$$

$$\frac{dY_p}{dt} = 0 \Rightarrow X(Y_T - Y_p) v_k(s) = (Y_p z) \times v_z$$

$$\Rightarrow Y_p = \frac{V_k(s) Y_T X}{(V_Z) Z + V_k(s) X}$$

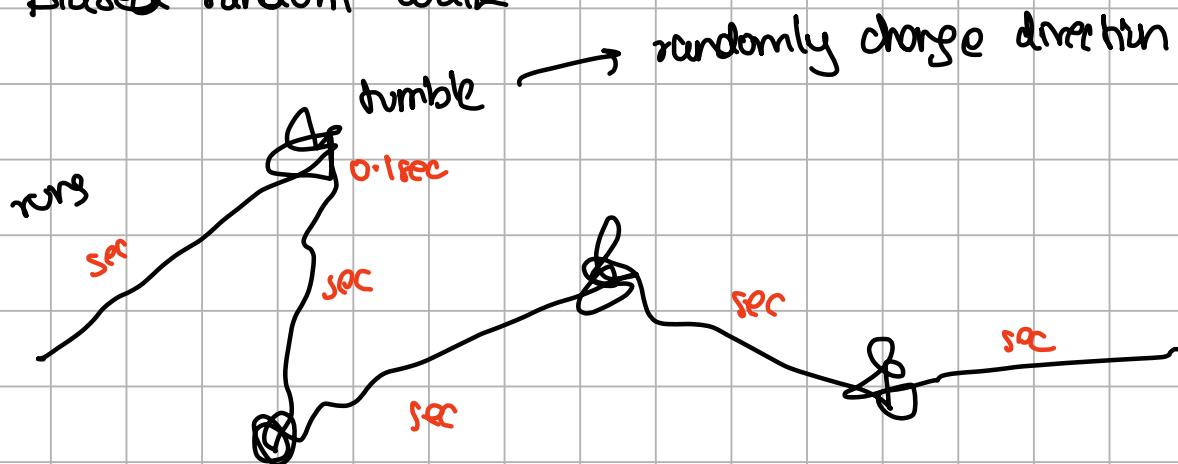


* Bacterial chemotaxis



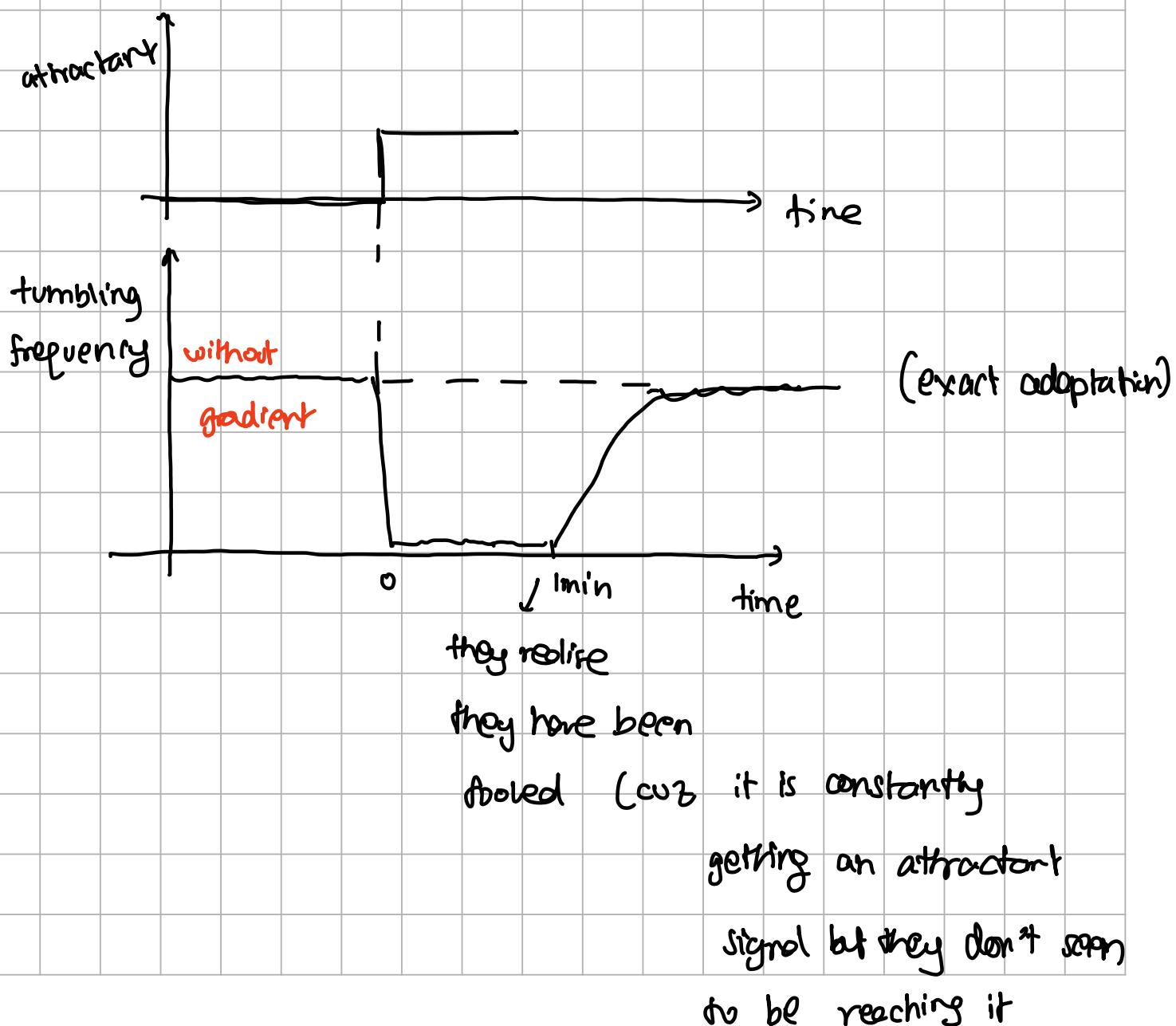
water keep colliding with them, so for a bacteria the environment is always like travelling through a storm

- Biased random walk



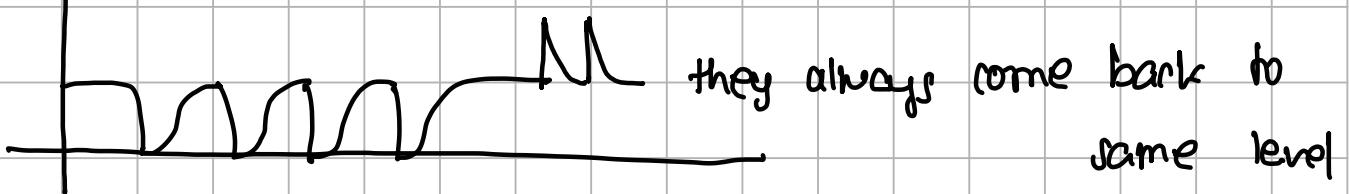
Now if you were to setup some sugar i.e. some gradient

- If the bacteria senses that it is sensing more sugar with time \rightarrow they reduce the probability per unit time of doing a tumble (reduce tumbling frequency)
- If the bacteria senses that it is sensing lesser sugar with time \rightarrow they increase their tumbling frequency





$\uparrow \uparrow \uparrow \uparrow$ (derivative's graph)



they always come back to
same level

if as if they only respond to the derivative,

if derivative becomes 0 they realize they have been fooled

and come back to normalcy

Perception

Say there were 1000 candles in a room

and I added 1 more, you wouldn't really

notice it in contrast to adding 1 candle when

there was only 1

\therefore Perception is relative to the background signal

we are adapted to.

† Weber's law -

background - so least noticeable difference - ΔS

then $\Delta S = K \beta$

say you were holding a 1kg and 1.001

then you would notice a change of 0.1kg

on top of that 1kg, and nothing lower.

if you were holding 0.1kg; you

would notice a change of 0.01kg

K is a different for different senses

(only within some range of so this is true)

too big - you might scratch your sensor

too small - you might not detect it)

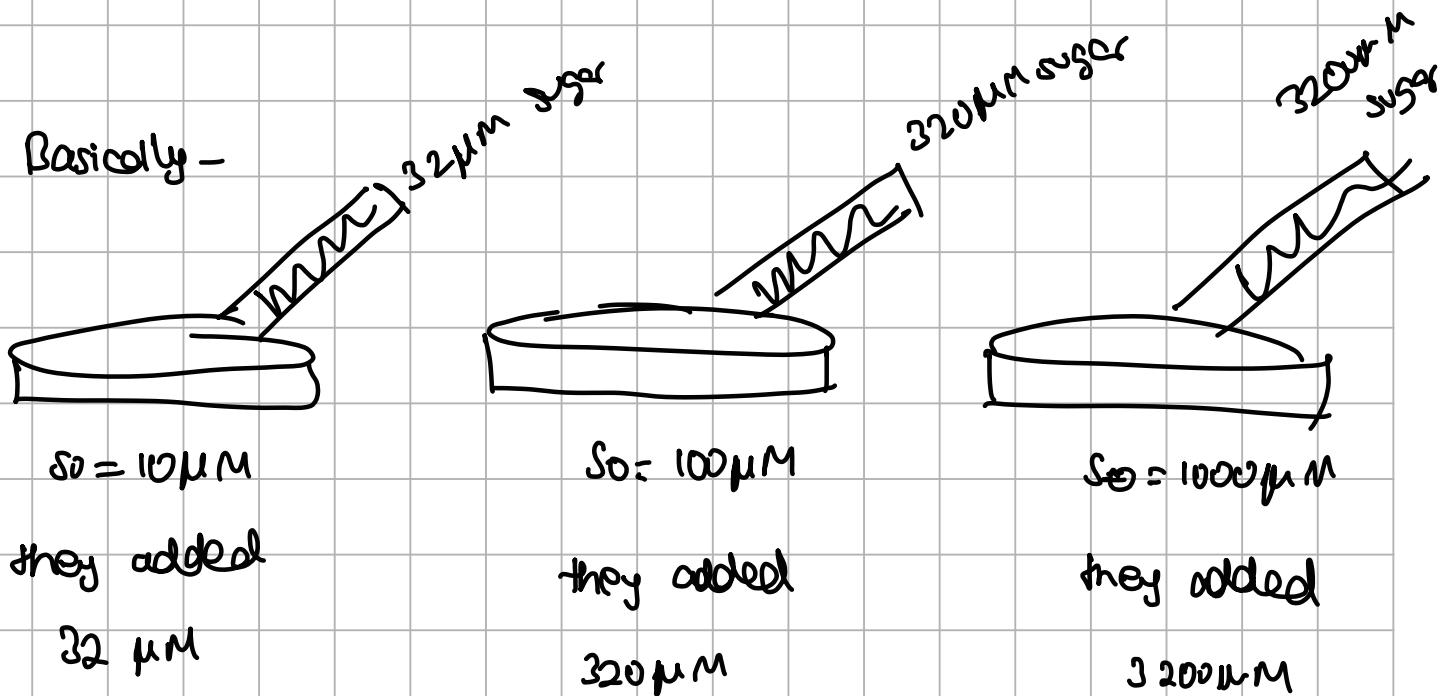
* Fold change detection circuitry

Example : Bacterial chemotaxis

Output : Tumbling frequency a

Input : Attractant concentration s

Basically -



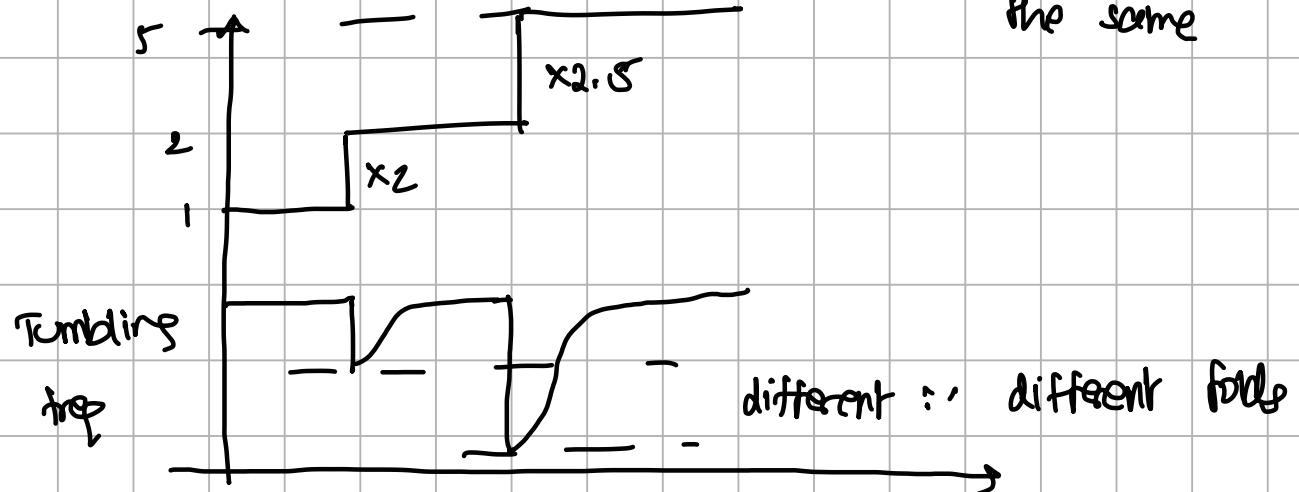
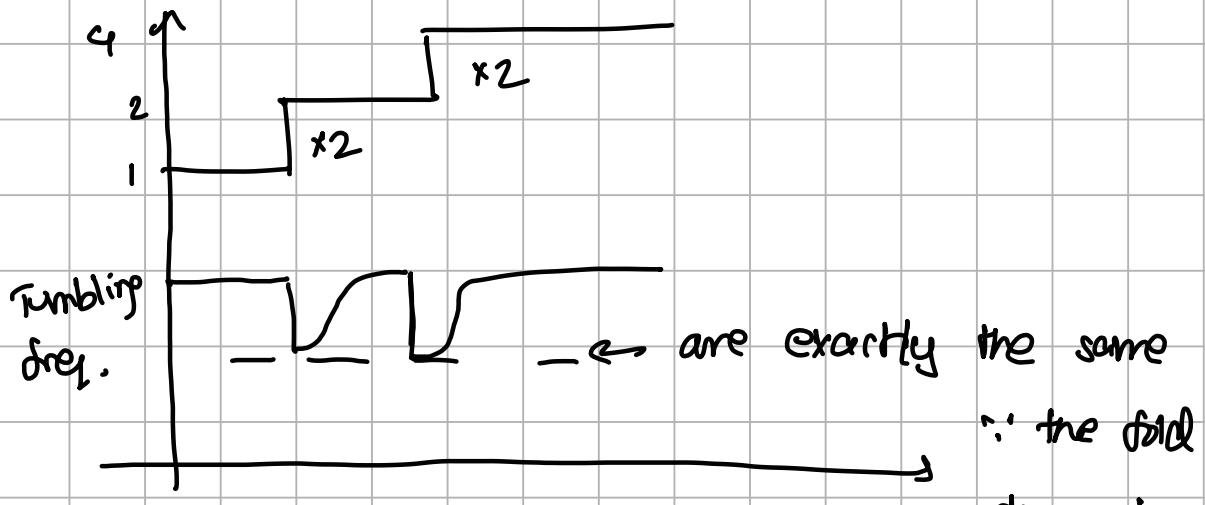
bacteria accumulated in the tube : a for all

for different folds however output was different

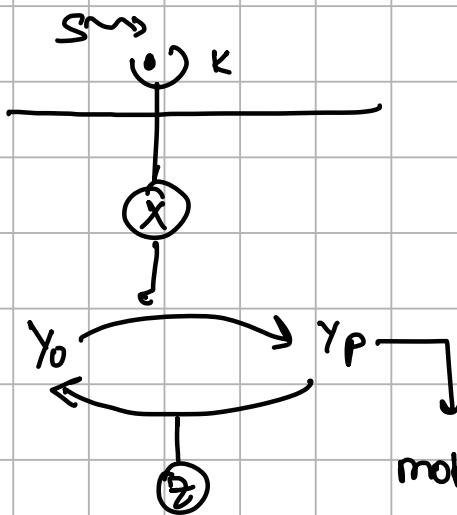
i.e if $s_0 = 10 \text{ } 30 \mu M$ vs $s_0 = 10 \text{ } 40 \mu M$

different amounts of bacteria

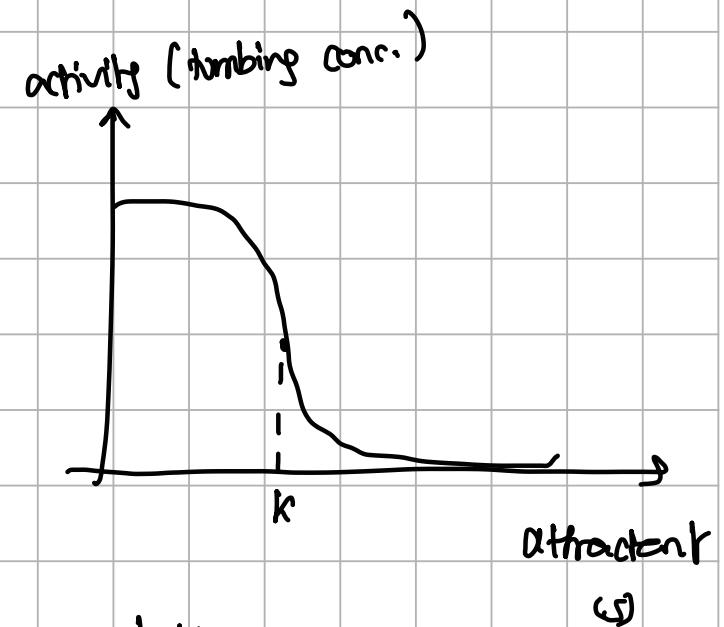
② FCD -



* How do they do it?

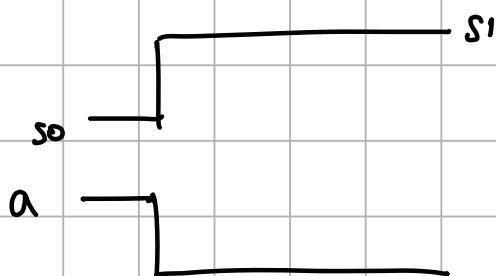
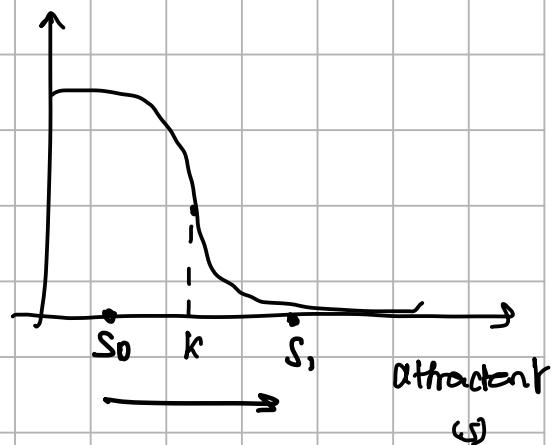


motors and hence tumble

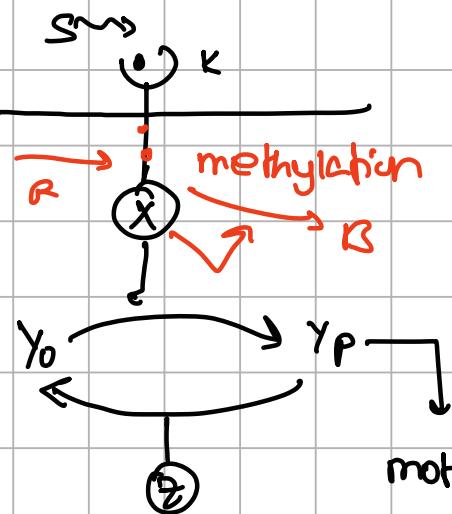


$$a = \frac{1}{1 + \left(\frac{S}{k}\right)^n} \rightarrow \frac{k^n}{S^n + k^n}$$

With only this mechanism



it would just decrease and stay there



methylation changes k

$$K = K_0 e^{\Delta G}$$

$$\Delta G = \Delta G_0 + \gamma_m$$

\uparrow each

methylation

adds a bit

of free energy

making the binding

harder $\therefore K \uparrow$

you need more

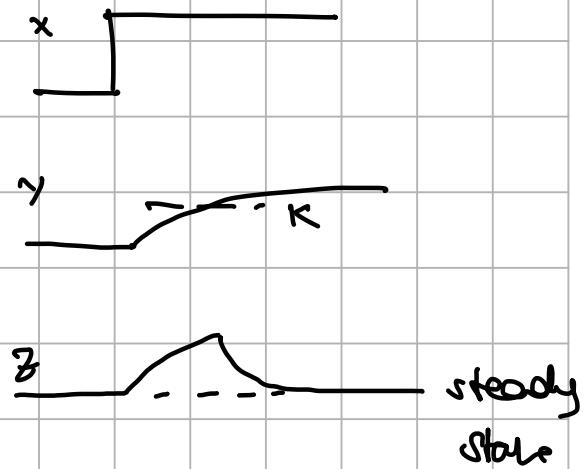
S for half activity

Basically $a = f(s/k)$

if s changes suddenly, a drops suddenly but then
 $k \uparrow$ slowly so that $f(s/k)$ is brought back

* Circuit 2 that can do fold change detection -

IFF



FCD \Rightarrow exact adaptation

x need not be the case

$$\frac{dy}{dt} = \beta_1 x - \alpha_1 y$$

$$\frac{dz}{dt} = \frac{\beta_2 x}{y + k} - \alpha_2 z$$

$\boxed{y \geq k}$ for FCD

steady state $\frac{dy}{dt} = 0 \Rightarrow y_{st} = \frac{\beta_1 x_{st}}{\alpha_1}$; y_{st} is proportional to $x_{st} \rightarrow$ bg

$$\frac{dz}{dt} = 0 \Rightarrow \alpha_2 z_{st} = \frac{\beta_2 x_{st}}{y_{st}}$$

$$\Rightarrow z_{st} = \frac{\beta_2 x_{st}}{\alpha_2 y_{st}}$$

$$= \frac{\beta_2 x_{st} \alpha_1}{\alpha_2 \beta_1 y_{st}} = \frac{\beta_2 \alpha_1}{\alpha_2 \beta_1}$$

so like if x_{st} is 10, y is ab 10 times
 x_{st} is 5, y is 5 times

$\therefore z_{st}$ is independent of the signal

This equation also possesses fold change detection

$$\frac{dy}{dt} = \beta_1 x - \alpha_1 y$$

$$\text{if } F = \frac{x}{x_0}$$

$$\frac{dz}{dt} = \frac{\beta_2 x}{y} - \alpha_2 z$$

$$\tilde{y} = y/x_0$$

equivalent

$$\frac{dz}{dt} = \beta_2 \frac{F}{\tilde{y}} - \alpha_2 z$$

$$\frac{d\tilde{y}}{dt} = \beta_1 F - \alpha_1 \tilde{y}$$

Both of these equations

depend only on F . \therefore

equivalent

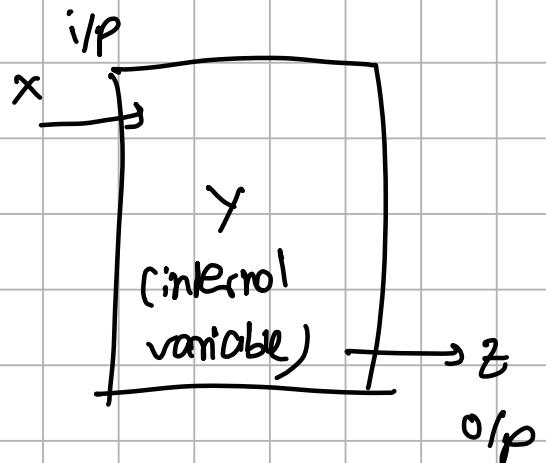
dynamics depends only on R (at least z 's dynamics
 icon comment
 idk y 's cut
 \tilde{x} dynamics is R
 dependent but
 $y = \tilde{y} x_0$; so
 depends on x_0)

General condition for fold change

lecture

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

$$\frac{dz}{dt} = (x, y, z)$$



Then FCD happens if following conditions are met

$$f(Lx, Ly, z) = Lf(x, y, z)$$

$$g(Lx, Ly, z) = g(x, y, z)$$

Homogeneity; allows

you to multiply by
any factor and keep
the diff eq. unchanged

ensures that z 's

dynamics remain
unchanged

yes y is getting L times

$$\text{bt } \frac{d(Ly)}{dt} = Lf(x, y, z) \therefore Ly \rightarrow \tilde{y} \text{ sub can be made}$$

↙ look at above proof if you are still confused

Building a biological oscillator

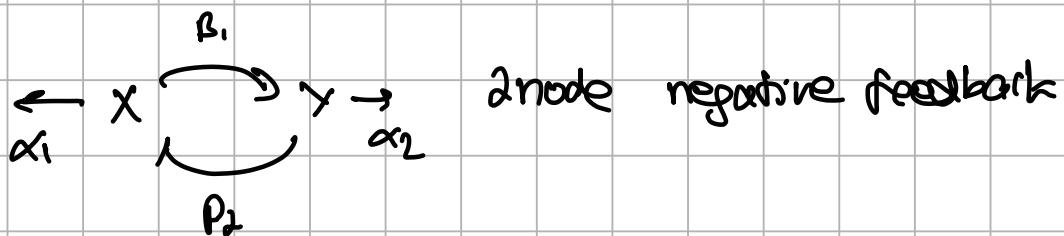
1. If its high \rightarrow low and repeat.

So this is more or less like a negative feedback loop

$\therefore G_x$ comes to mind, however we require some delay for it to be an oscillator else it will cutoff and hit steady state

perfectly

Therefore delay is necessary

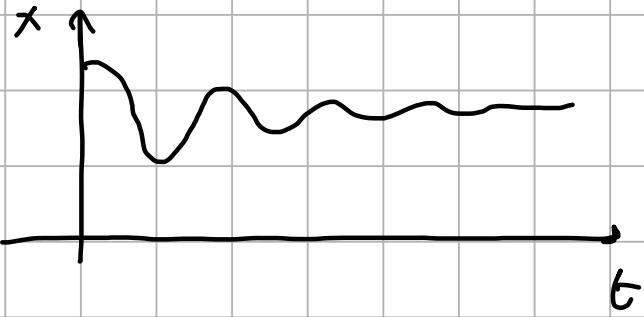


$$\frac{dx}{dt} = f(y) - \alpha_1 x$$

decreasing function

$$\frac{dy}{dt} = g(x) - \alpha_2 y$$

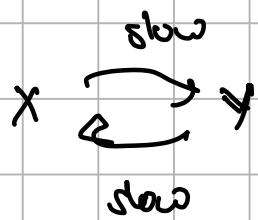
increasing function



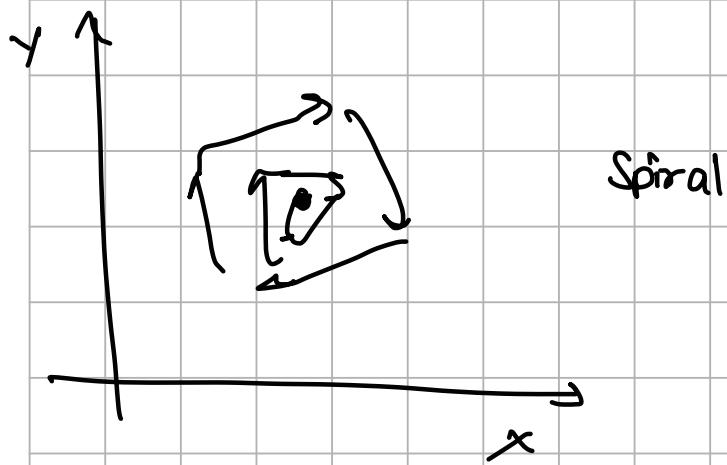
But we will now
have sustained oscillations

:(

$\alpha_1 \sim \alpha_2$ ie both should have similar timescales



if either one is
fast then in terms of
time it is basically

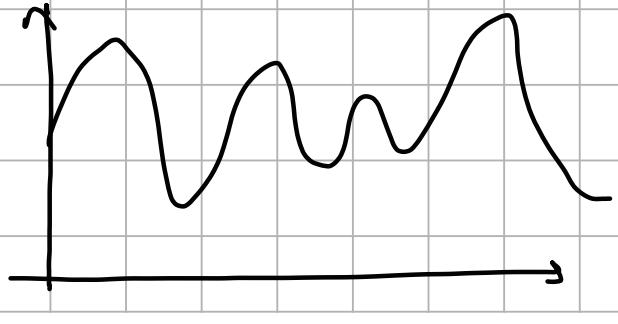
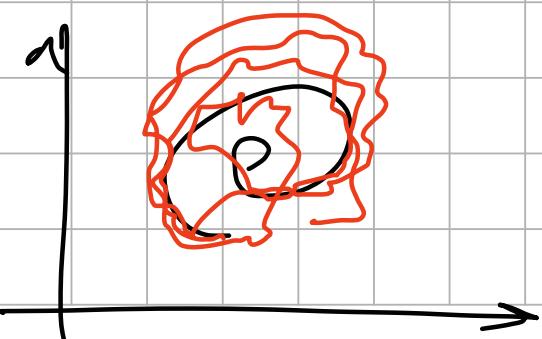


slow
fast
('cos this is
no time)

Say if there was some noise - it would prevent

it from reaching the fixed point - always kicking it here

and there - incoming oscillations



noise + damped oscillations = oscillators

* A more profound model for biological oscillators -



- tunable frequency with same amplitude