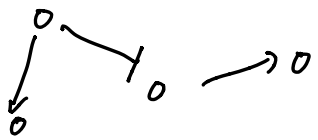
Central dogma 1958 Crick

"Flow of information"

DNA → RNA → Protein

unit

⇒ Notion of gene networks

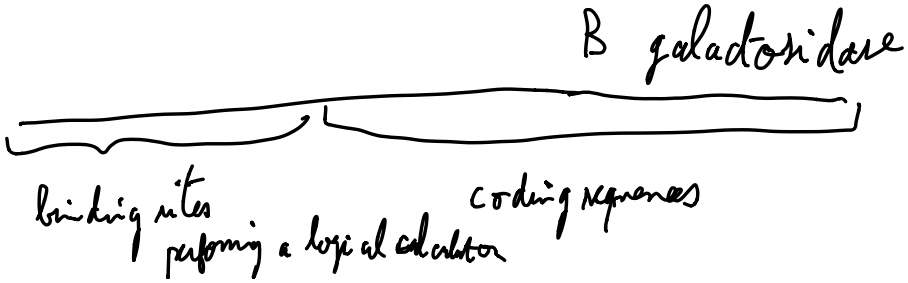


They process information (in a loose sense)

Classical example: Lac Operon

J. Mol. Biol. 1961

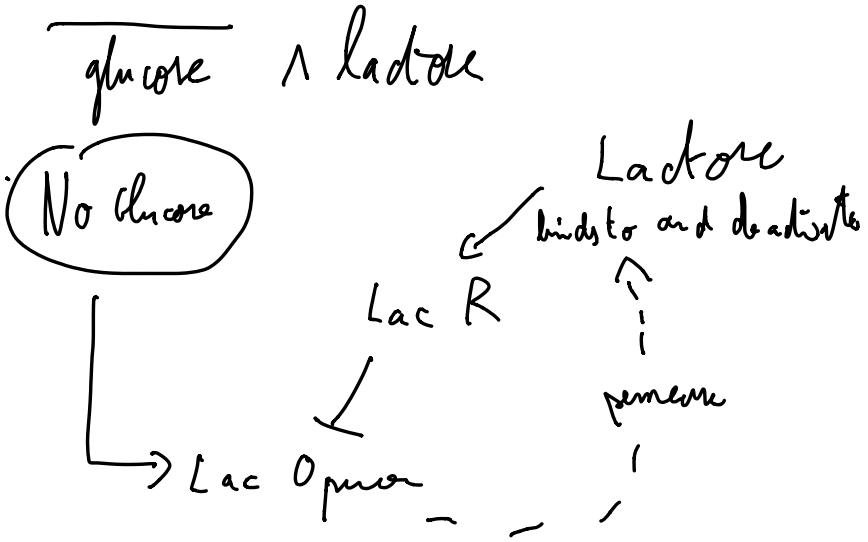
E coli : change of sugar ⇒ glucose from lactose



A repressor: LacR. If no lactose, repressor is here ⇒ no transcription

An activator: cAMP, here only if glucose is absent.

This is our first example of information processing: this is a logical gate performing the computation



Now there is a catch

Novick and Wiener, 1957:

Enzyme induction as a "all or none phenomenon"

There is a positive feedback

This creates cellular memory : once you induce, even low concentration of lactose ensure that you stay on.

"all the progeny of an induced bacterium are induced as long as maintenance inducer is present"

⇒ information processing over several generations.

Fast Forward until the early 2000s

- genome sequencing made easy
- genetic engineering easier

...

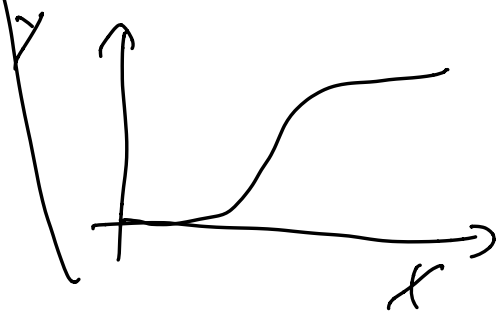
one can start :

- mapping all these logical interactions
- synthetizing new constructs / dynamics based on rational designs
- more theory

Building blocks: activations / repressions

$X \to Y$

$\dot{Y} = \dfrac{\beta X^n}{X^n + X_0^n} - \gamma Y$



$X \dashv Y$

$\dot{Y} = \dfrac{\beta}{1 + \left(\frac{X}{X_0}\right)^n} - \gamma Y$

Network motifs Uri Alon

Milo et al, 2002

Shen-Orr et al, 2002

Idea: . take networks

. randomize connections

. look for statistically over-represented networks

A first motif: "autoregulation"

# nodes	# edges
E. Coli:	
400 nodes	500 edges
Yeast: 700 nodes	~1000 edges

10%! you would roughly expect $400 \times \frac{1}{400} \sim 1$

(40 in E. coli)

only the direct ones

there are indirect ones

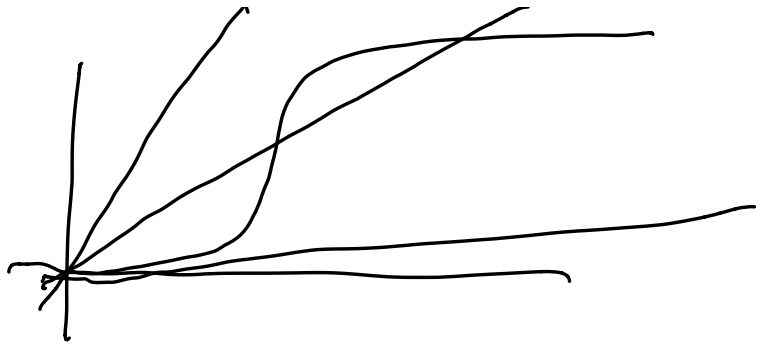
What could be their dynamical functions?

Let us start with

An interesting feature: multistability

$$\dot{X} = \underbrace{\frac{\beta X^n}{X^n + X_0^n}}_{\text{production}} - \underbrace{\lambda X}_{\text{degradation}} = -\partial_X V(X)$$

Multistability: let us solve $\dot{X} = 0$ (existence of potential)

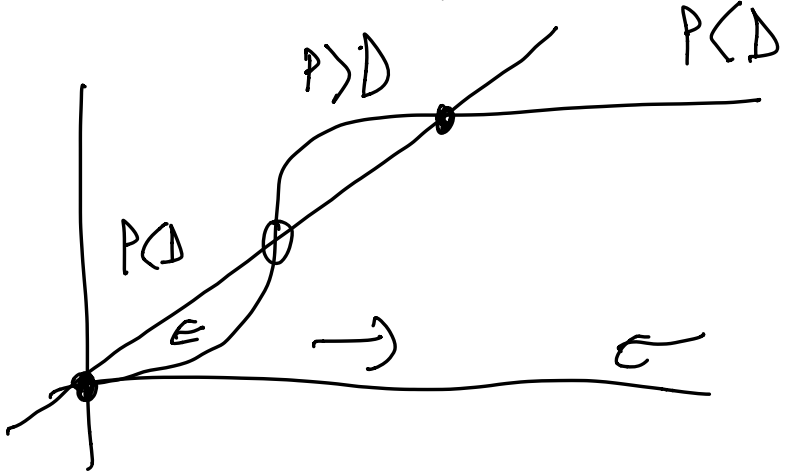


$1 \to 3 \to 1$ (2 if tangent)

0 always is a steady state

a pair a steady state can appear.

What about their stability?



There is a high steady state.

Depending on the initial conditions, the system can

stabilize in either of these. "Memory"

Epigenetic state.

Motif is very important for differentiation, e.g.

TERMINAL SELECTOR GENE

Olivier Hobert, PNAS 2008

ASE sensory neurons CHE-1

AST-1 dopaminergic neurons

MyoD ⇒ myogenesis

one variant

$A \rightleftharpoons B$

Of course important for cell reprogramming

Problem: more I think Boltzmann $P(x) \propto e^{-\beta V(x)}$ ⇒ you will

Cis vs trans: check Martin Howard more

You can lock in the long term with

epigenetic markers (e.g. methylation)

Martin Howard & Caroline Dean

Polycomb silencing, Science, 2017

$$\dot{X} = \frac{\beta}{1+\left(\frac{X}{X_0}\right)^n} - \mu X$$

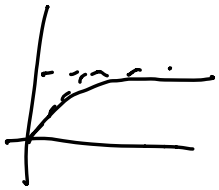
obviously monostable. More interesting: dynamics

2 interesting effects:

- speed-up of response
- oscillations

Response speed-up (Rosenfeld, Elowitz, Alon, J Mol Biol 2002)

Imagine $\dot{X} = \lambda - \delta X$



$X(t) = \frac{\lambda}{\delta}(1 - e^{-\delta t})$ time-scale : $\frac{1}{\delta}$

Compare with $\dot{X} = \frac{\beta}{1 + \frac{X}{X_0}} - \delta X$

Assume $\dot{X} \sim \frac{\beta X_0}{X} - \delta X$

$\frac{1}{2}\frac{d}{dt} x^2 = \beta X_0 - \delta x^2$

$x^2(t) \sim \frac{\beta}{\delta}\left(1 - e^{-2\delta t}\right)$

$X(t) \sim \sqrt{\frac{\beta}{\delta}\left(1 - e^{-2\delta t}\right)}$

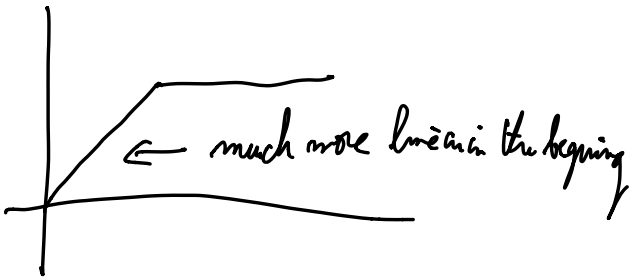
Half steady-state concentration: $1 - e^{-2\delta t} = \frac{1}{4}$

$2\delta t = \ln \frac{4}{3}$

$t = \frac{1}{\delta}\frac{1}{2}\ln\frac{4}{3} \sim 0.21\,\delta$

$\Rightarrow \times 5$ faster

(Intuitively



More interesting: oscillators.

For this we need a delay. No lack of this in biology (transcription, translation, etc...)

Ex $\dot{X} = f(x(t-\tau)) - \delta X$

explicit delay (Glass, Mackey, 70's; Julian Lewis, Curr Biol, 2003)

Goodwin model

$X \to Y \to Z$

$\dot{X} = \frac{k_x}{1+Z^n} - \delta_x X$

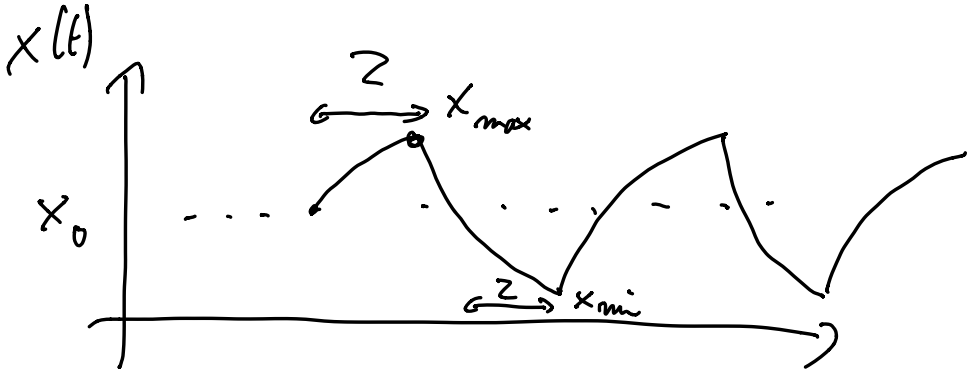
$\dot{Y} = k_y X - \delta_y Y$

Skip

Let us start with delayed model, infinite" equation

$$f\left(x(t-\tau)\right) = \begin{cases} 0 \text{ if } x(t-\tau) \geqslant x_0 & \dot{x} = -\delta x \\ \rho \text{ if } x(t-\tau) < x_0 & \dot{x} = \rho - \delta x \end{cases}$$

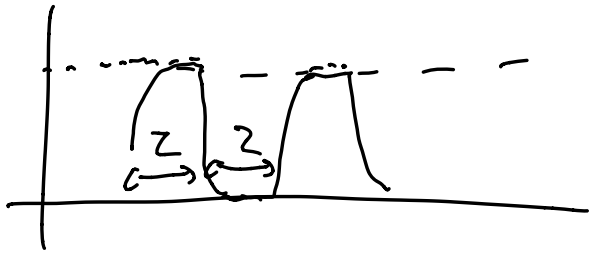
(to do this, take $\dfrac{\rho}{1+\left(\frac{x}{x_0}\right)^n} \xrightarrow[n\to\infty]{} f$)



You can compute x_{max} and x_{min} in a self consistent way.

As well as the period.

If $\rho, \delta \gg 1$



Period $\sim 2\tau$. You can then easily compute first order correction

$$T \sim 2Z + \frac{K}{\delta} + \cdots \qquad \delta \gg 1$$

$$K = \ln \frac{r^2}{r-1} \qquad r = \frac{l}{X_0 \delta} > 1$$

(PF, Hakim, PRE 2005)

More complicated networks

Feed Forward Loop

All arrows can be positive and negative.

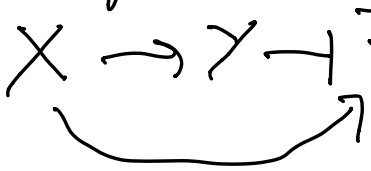
Mangan & Alon, 2003, PNAS

"coherent" same signs

eg $X \to Y \to Z$ (with $X \to Z$)

~ 30 : both E. Coli and Yeast

Incoherent e.g.

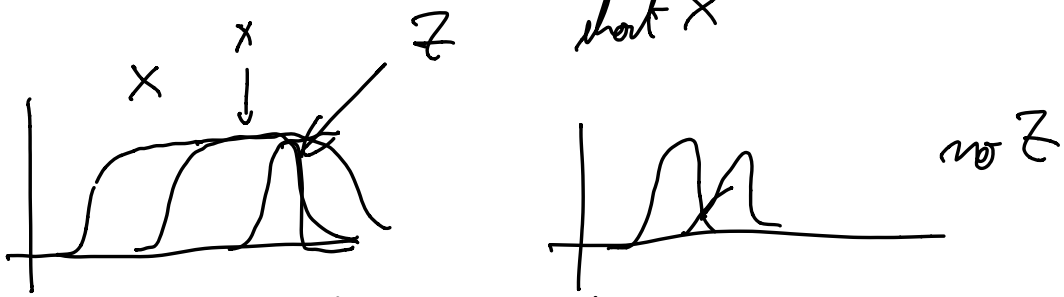


5 in E. Coli

21 in Yeast

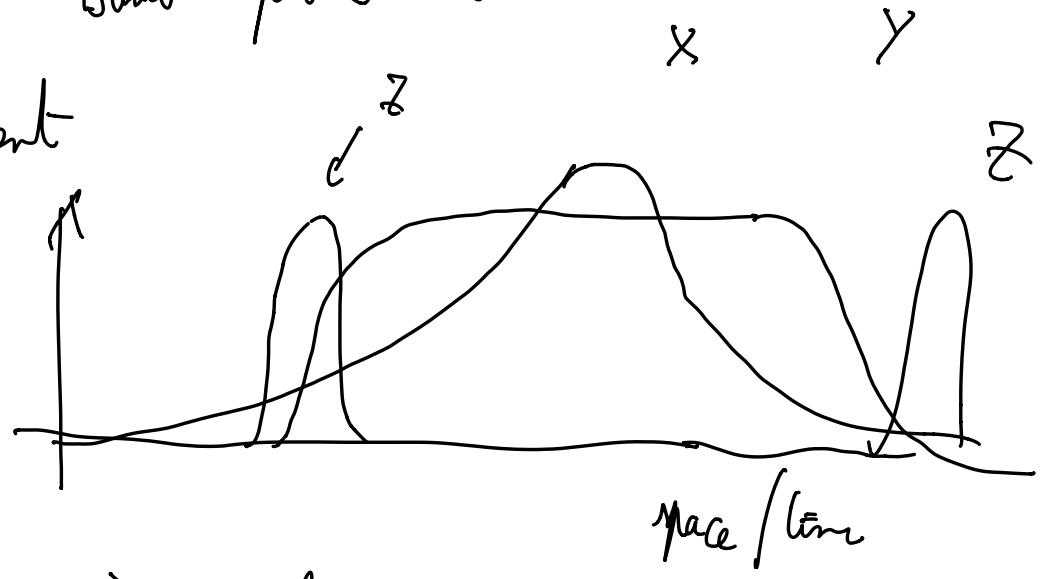
Fantional role?

Coherent: "persistence detector"



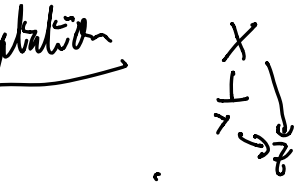
"Dumb" phones work like this

Incoherent



"stripe" module

Adaptation



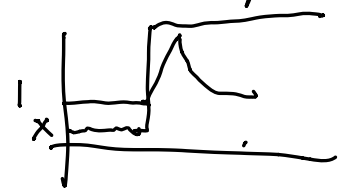
$\dot{z} = f(x)\, y - z$

$\dot{y} = \frac{1}{f(x)} - y$

steady state

$z = 1$ independent of x

But this induces delay



when x increases $\Rightarrow f(x)$ bigger
but y did not change yet
so $z \longrightarrow$ increases

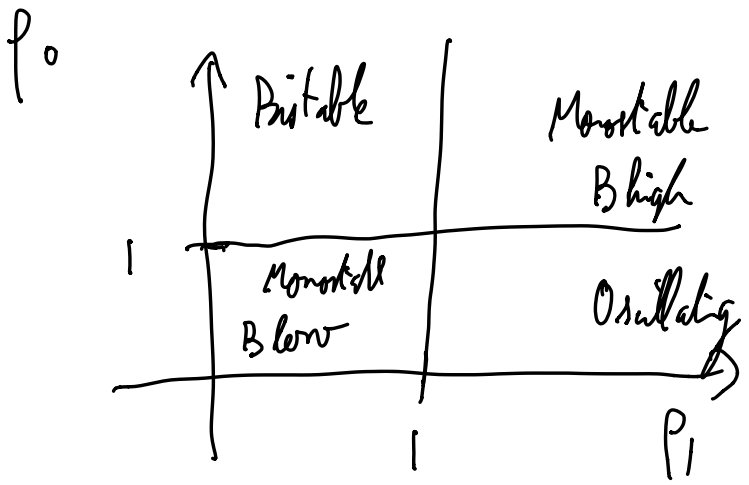
For instance: if we add Protein Protein interaction or allostery, one can do different tricks Yeqa. Eaton, PNAS 2002

The Mixed Feedback Loop

$A \longrightarrow B$ or $A \dashv B$

$A + B \longrightarrow C$, unable to regulate B

Phase diagram (PF & Hakim, PRE, 2005)



(limit where $A+B \to C$ super fast)

ρ_0: rescaled production rate of B vs A when A is unbound

ρ_1: ——————— A bound

You could imagine system where ρ_1 and ρ_0 are regulated so that you go from oscillating to bistable. There are ∞ ways to do that but ∞ pathways would give you ∞ interesting dynamics (in particular if you go through the critical point)

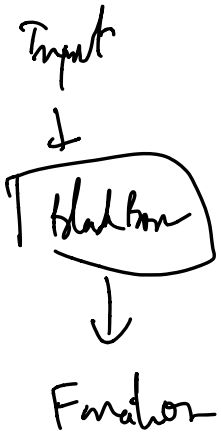
Example: Lac operon

circadian clocks.

Fly PER:TIM ≡ B
CYC:CLK ≡ A
Mammals PER:CRY
CLK:BMAL

Here I look a very much structure/function approach. A reason is that there are examples of the networks working like this. But it does not mean they are like this for this function.

Another aspect: modularity



But we can clearly identify modules, and if we believe there are functional, why don't we see more interpretable things

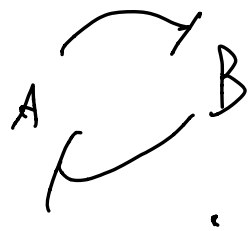
Answer: variation of selective pressure

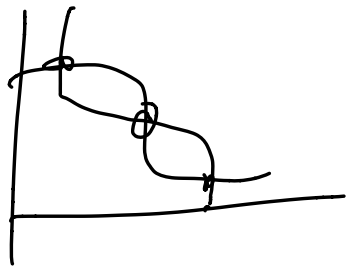
Emergent e.g. f ∧ g alternating f ∨ g

"mode preserving" ⇒ to know f, g, then right some limits.

Known made modules

Toggle Switch





$$\dot{B} = \frac{A_0^n}{A_0^n + A^n} - \lambda B$$

$$\dot{A} = \frac{1}{1 + C\left(\frac{A_0^n}{A_0^n + A^n}\right)^m} - \lambda A$$

$$\sim \frac{\left(A_0^n + A^n\right)^m}{\left(A_0^n + A^n\right)^m + C A_0^{nm}} - \lambda A$$

Les effectifs positifs feedback

Représentation