Lecture 13: Genomes

Goal: Model interactions between gene regulatory elements, discuss common motifs in genetic circuits

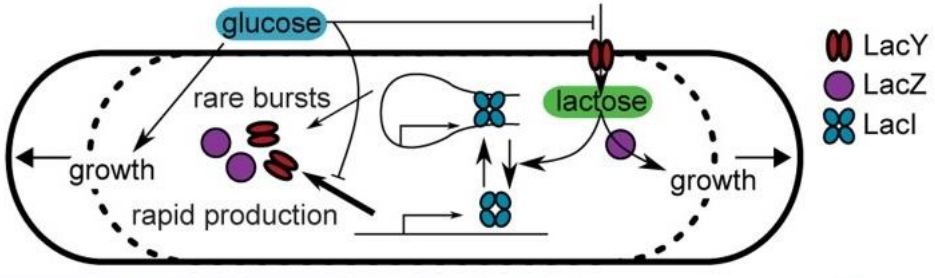
- Genetic switches
- Genetic oscillators

Reading: PBOC Chapter 19.3.2, 19.3.3

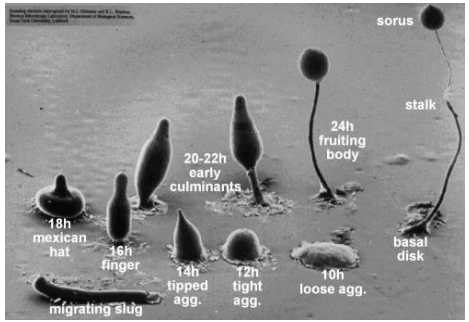
Genomes

How do cells make decisions?

- Even simple organisms make complex decisions
- Cells respond to stimuli by producing proteins
  - Stimulus: sugar. Response: make proteins to digest sugar. + repress others
  - Stimulus: DNA damage. Response: make DNA repair proteins.
- How much to make, and when to make it?
- Single cells lack an obvious "brain"
- How is the computation achieved?



Escherichia coli



Dictyostelium discoideum

input signal: stimulus

processing: genetic circuits

output: change in protein expression

Gene regulation

Elements of genetic circuits

Structural Genes - code for protein and RNA molecules that are required for normal enzymatic or structural functions in the cell.

Regulatory Genes - code for protein and RNA molecules whose function is to regulate the expression of other genes. “Transcription factors”

Numbers: ~1600 transcription factors vs. ~20,000 protein coding genes in human genome

~ 10% of human genes encode for regulatory function!

Gene regulation

Elements of genetic circuits

Monod (Nobel Laureate 1965)

The biochemical processes that take place within an organism's cells are controlled by the genes found inside DNA molecules. Jacques Monod and François Jacob proved how the genetic information is converted during the formation of proteins by means of a messenger, which proved to the substance we now know as RNA. Different cells work in different ways at different times, however. This too is regulated by genes. In the early 1960s Monod and Jacob mapped the intricate processes that determine how genes are expressed or suppressed in a self-regulating process.

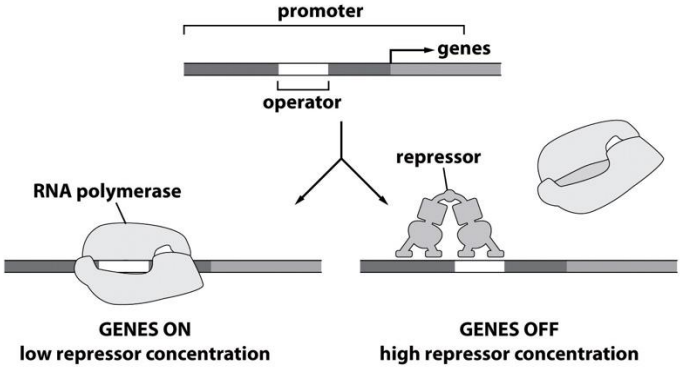
"Tout ce qui est vrai pour le Colibacille est vrai pour l'éléphant."

Genome regulation

Recall:

Genetic networks: Molecules

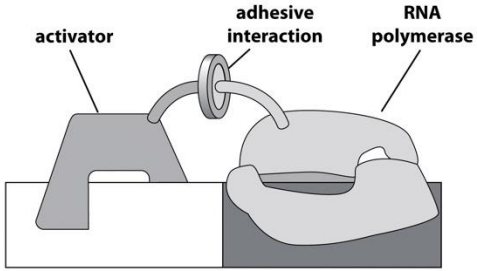
negative regulation



X ⊣ Y

"simple regulation"

positive regulation



X → Y

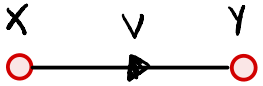
Repressors and activators change the probability of RNA polymerase binding to the promoter of a gene

Genome regulation

Recall:

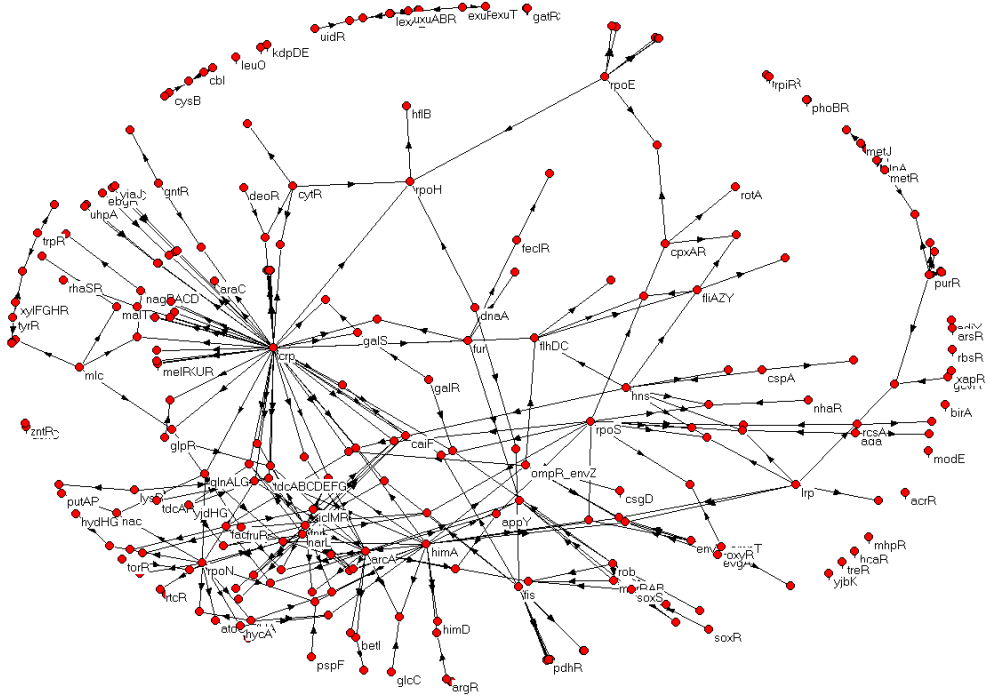
Genetic networks: E. coli transcription

each edge has a direction, a sign, and a numerical value



$v > 0$ $X \rightarrow Y$

$v < 0$ $X \dashv Y$

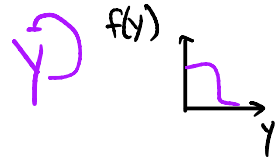


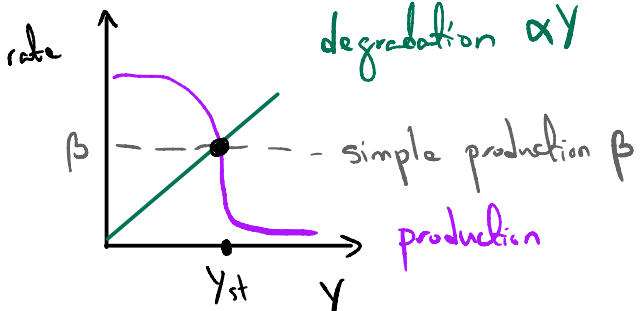
Genome regulation

Recall:

Genetic networks: Molecules

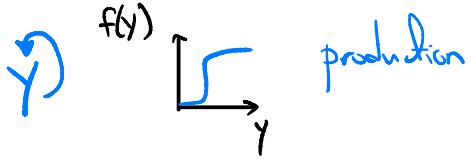
negative autoregulation

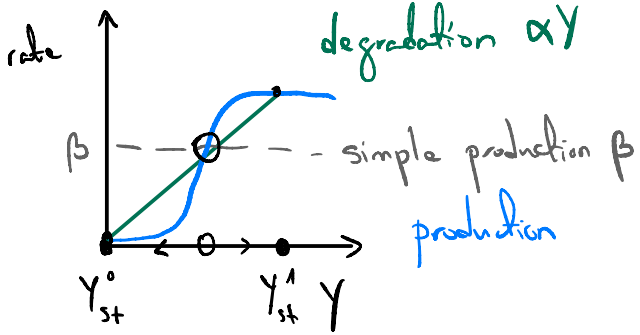




Single, global fixed point

positive autoregulation

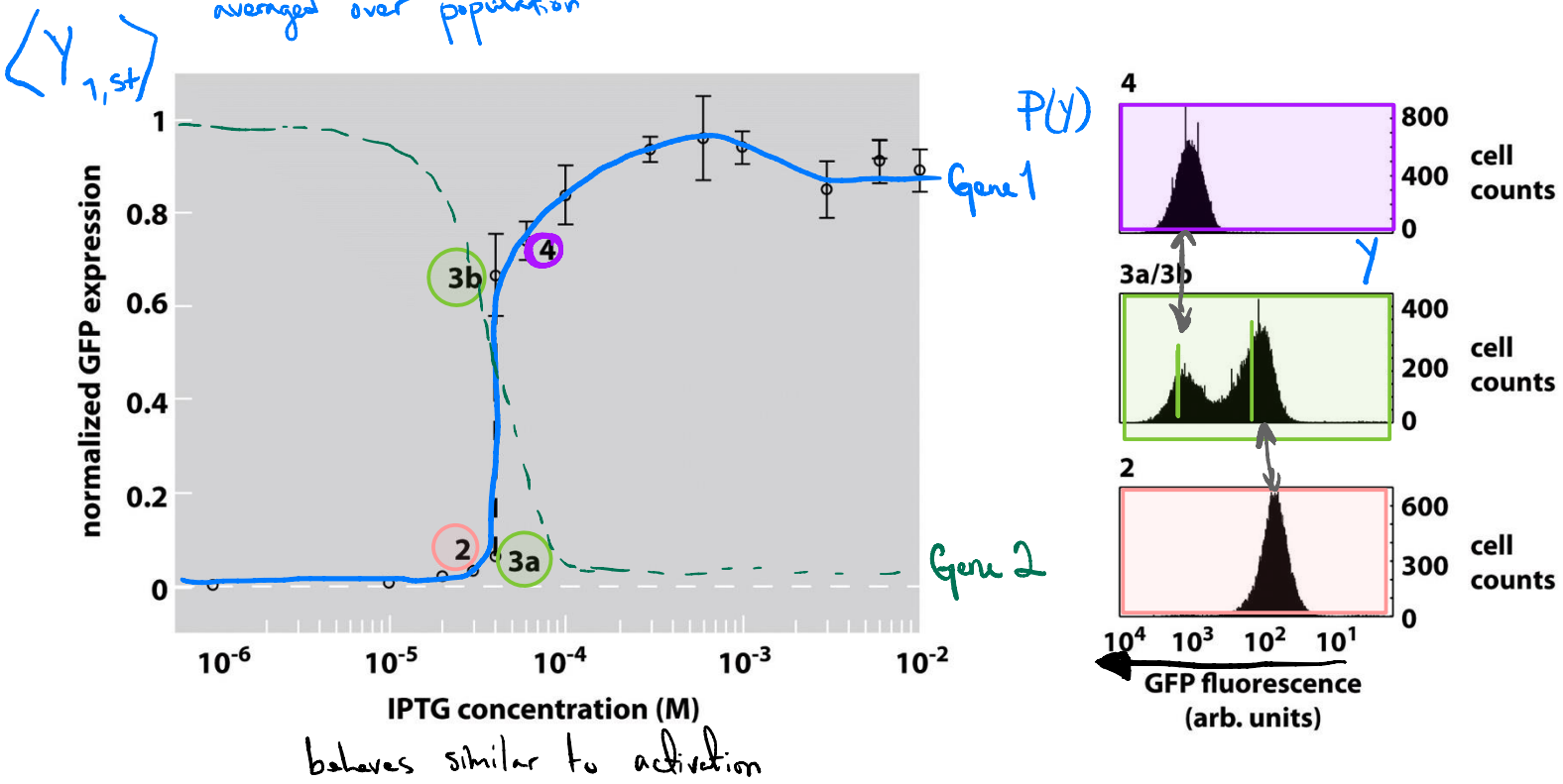




One or two stable fixed points
Zero or one unstable fixed points

Genome regulation

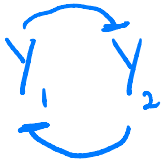
Genetic networks: Switches

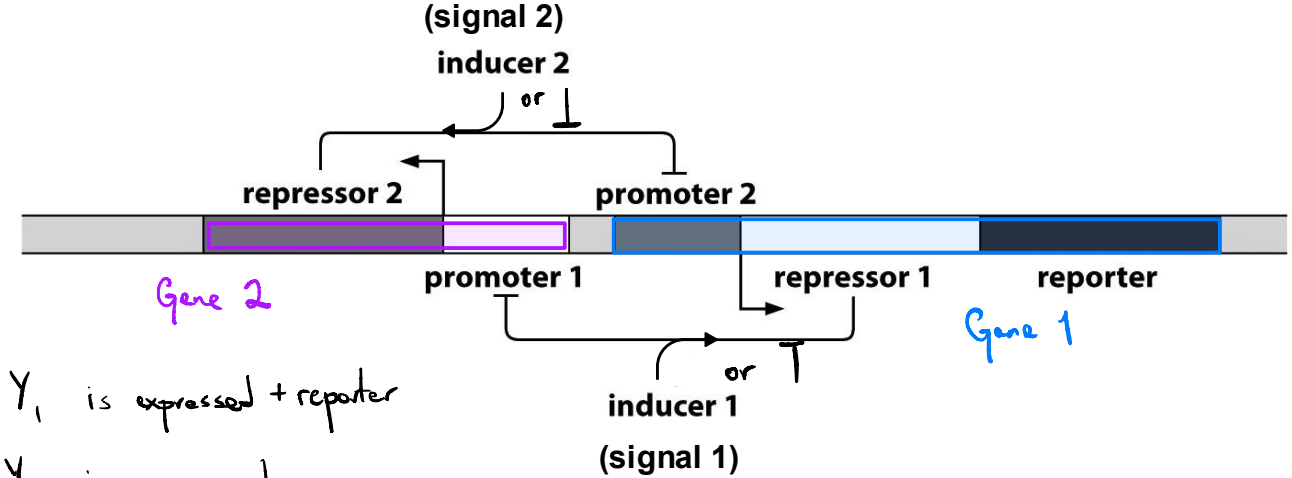


Genome regulation

Genetic networks: Switches

Circuit





If $S_1 \Rightarrow Y_1$ is expressed + reporter

Y_2 is repressed

If $S_2 \Rightarrow Y_2$ is expressed

Y_1 is repressed

Exercise: Write down differential equations governing C_1 and C_2, concentrations of Y_1 and Y_2.

$\frac{dc_1}{dt}$; $\frac{dc_2}{dt}$

Goal: Model time dependence of c_1, c_2.

Processes: degradation, production, and repression.

$$\frac{dc_1}{dt} = \underbrace{\gamma}_{\text{production}} - \underbrace{\gamma p_{bound}(c_2)}_{\text{repression}} - \underbrace{k c_1}_{\text{degradation}}$$

Note: $p_{bound}(c_2) = \dfrac{K_b c_2^{\,n}}{1 + K_b c_2^{\,n}}$

Hill function, coefficient n.

Goal: Model time dependence of c_1, c_2.

Processes: degradation, production, and repression.

$$\frac{dc_1}{dt} = \underbrace{\gamma}_{\text{basal production}} - \underbrace{\gamma\, p_{bound}(c_2)}_{\text{repression}} - \underbrace{k c_1}_{\text{degradation}}$$

$$= \frac{\gamma}{1 + K_b c_2^{\,n}} - k c_1$$

Similarly, $$\frac{dc_2}{dt} = \frac{\gamma}{1 + K_b c_1^{\,n}} - k c_2$$

Note: $p_{bound}(c_2) = \dfrac{K_b c_2^{\,n}}{1 + K_b c_2^{\,n}}$

Hill function, coefficient n.

Assumption: degradation rate is the same for both proteins.

For proteins with $\frac{1}{k} > t_{cell\ cycle}$, dilution is main effect.

Assumption: basal production rate is the same. Not always true.

Goal: Model time dependence of c_1, c_2.

Processes: degradation, production, and repression.

$$\frac{dc_1}{dt} = \underbrace{\gamma}_{\text{basal production}} - \underbrace{\gamma p_{bound}(c_2)}_{\text{repression}} - \underbrace{Kc_1}_{\text{degradation}}$$

$$= \frac{\gamma}{1+K_b c_2^n} - Kc_1$$

Similarly, $$\frac{dc_2}{dt} = \frac{\gamma}{1+K_b c_1^n} - Kc_2$$

Simplify: $$\frac{du}{dt} = -u + \frac{\alpha}{1+v^n}$$

$$\frac{dv}{dt} = -v + \frac{\alpha}{1+u^n}$$

Note: $p_{bound}(c_2) = \dfrac{K_b c_2^n}{1+K_b c_2^n}$

Hill function, coefficient n.

Assumption: degradation rate is the same for both proteins.

For proteins with $\frac{1}{K} > t_{cell\ cycle}$, dilution is main effect.

Assumption: basal production rate is the same. Not always true.

units of c_1 and c_2 are $K_b^{-1/n}$

units of time are K^{-1}

$\alpha = \gamma K_b^{1/n}/K$

Steady state: $\frac{du}{dt} = 0 = -u^* + \frac{\alpha}{1+v^{*n}}$ $\frac{dv}{dt} = 0 = -v^* + \frac{\alpha}{1+u^{*n}}$

A solution: $u^* - \frac{\alpha}{1+(u^*)^n} = v^* - \frac{\alpha}{1+(v^*)^n}$

symmetry $u^* = v^*$

This is not a switch, two concentrations are equal.

Steady state: $\frac{du}{dt} = 0 = -u^* + \frac{\alpha}{1+v^{*n}}$ $\qquad$ $\frac{dv}{dt} = 0 = -v^* + \frac{\alpha}{1+u^{*n}}$

A solution: $u^* - \frac{\alpha}{1+(u^*)^n} = v^* - \frac{\alpha}{1+(v^*)^n}$

This is not a switch, two concentrations are equal.

$$u^* = v^*$$

Other solutions of the form $v^* = f(f(v^*))$ where $f(v^*) = \frac{\alpha}{1+(v^*)^n}$

Demonstration: $-u^* + \frac{\alpha}{1+v^{*n}} = 0 \Rightarrow u^* = \frac{\alpha}{1+(v^*)^n}$ Substitute into $v^* = \frac{\alpha}{1+(u^*)^n}$

General expression, find the roots

Particular case: $n = 2$ $\quad u^* = \frac{\alpha}{1+\left(\frac{\alpha}{1+(u^*)^2}\right)^2}$ $\qquad$ $v^* = \frac{\alpha}{1+\left(\frac{\alpha}{1+(v^*)^2}\right)^2}$

Factor: $\underbrace{\left((u^*)^2 - \alpha u^* + 1\right)}_{\text{parabola}}\underbrace{\left((u^*)^3 + u^* - \alpha\right)}_{\text{cubic}} = 0$

parabola: zero, one, two real roots ($\alpha<2$) ($\alpha=2$) ($\alpha>2$)

cubic: one real root

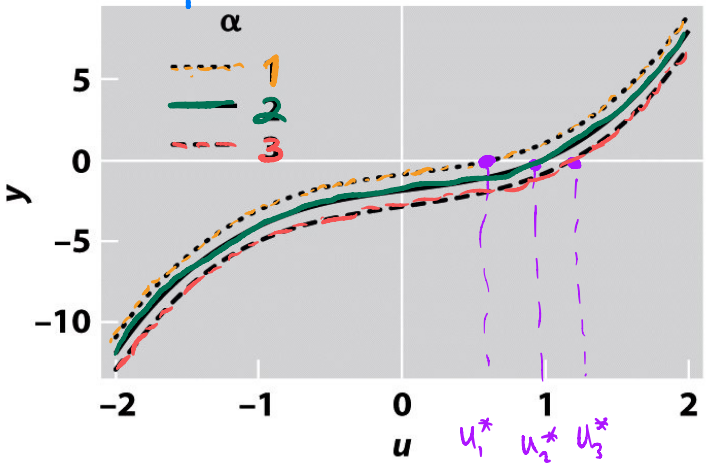
Genome regulation

Genetic networks: Switches

cubic factor

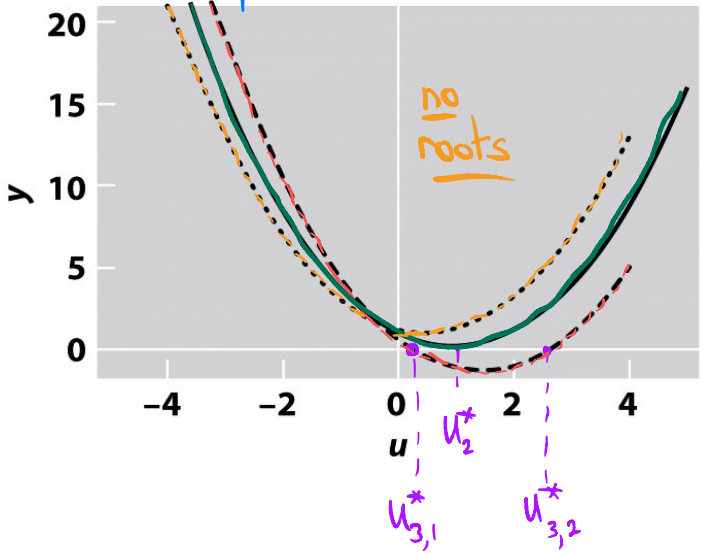
$y = (u)^3 + u - \alpha$

steady-state solutions:



parabolic factor

$y = (u)^2 - \alpha u + 1$



Root: $u^* = \frac{\alpha}{1+(u^*)^2} \overset{\text{previously}}{=} v^*$

two concentrations are equal.

For a given solution $u_{3,1}^*$, v^* takes other root. $u_{3,2}^*$

SWITCH!

Genome regulation

Genetic networks: Switches

Stability analysis:

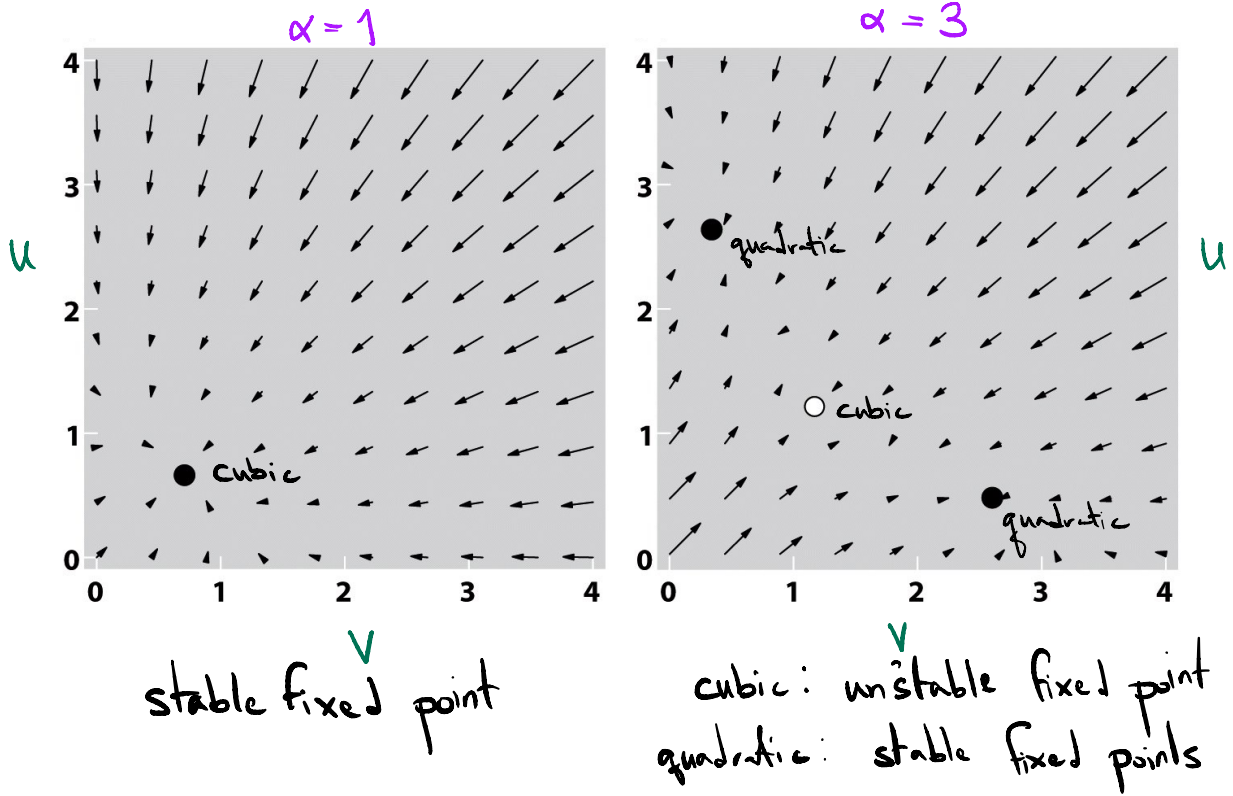
phase portrait

$\frac{du}{dt}$ and $\frac{dv}{dt}$ vector components

steady state, vectors are zero

stable fixed points return from small perturbations

(vectors point toward)



stable fixed point

cubic: unstable fixed point

quadratic: stable fixed points

Genome regulation

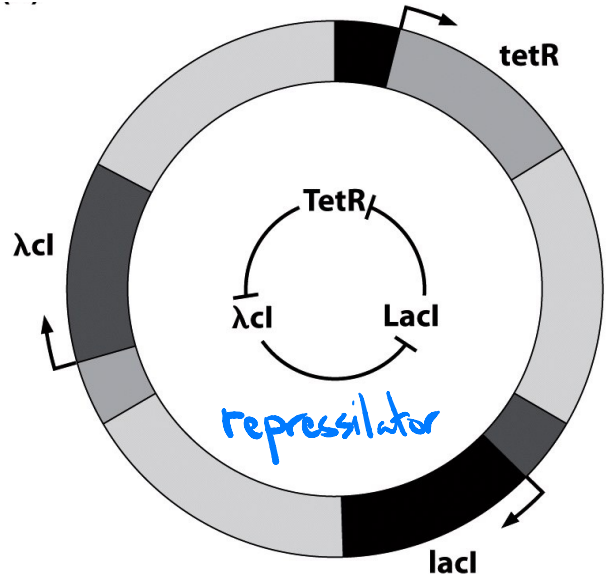
PBoC 19.3.3

Genetic networks: Oscillators

Example: cell cycle, circadian rhythm.

How does one possible circuit look, for an oscillator?

Three interacting promotors.

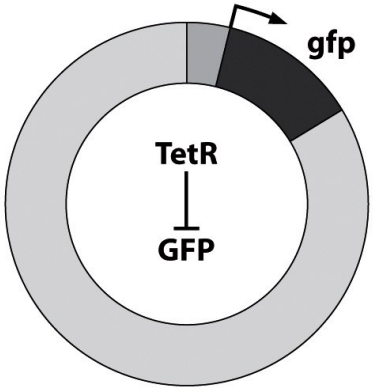


TetR acts on λ_{cI}.

λ_{cI} acts on LacI.

LacI acts on TetR.

reporter, GFP expressed when TetR is absent.



Genome regulation

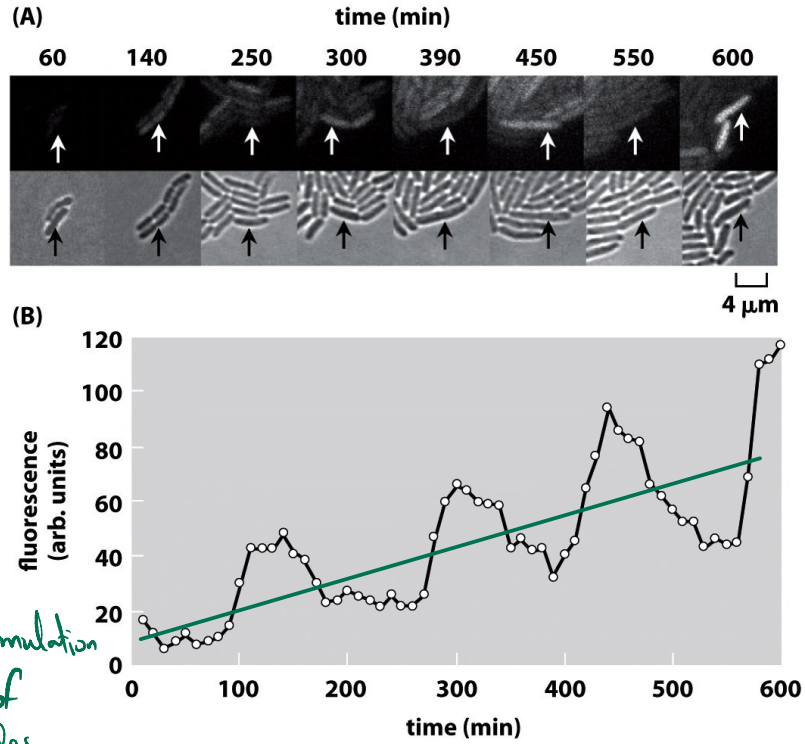
Genetic networks: Oscillators

Put into E. coli. Take images of cells.

movie

Average fluorescence in a single cell.

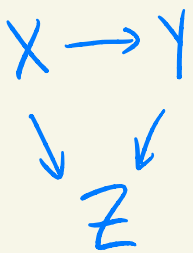
Can again write down coupled differential equations for each species.



protein accumulation

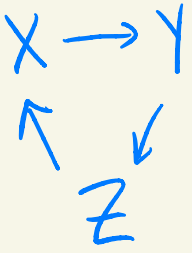
poor separation of timescales

What kinds of simple circuits can you construct from three nodes?



feed forward loop

In E. coli: 42



feedback loop

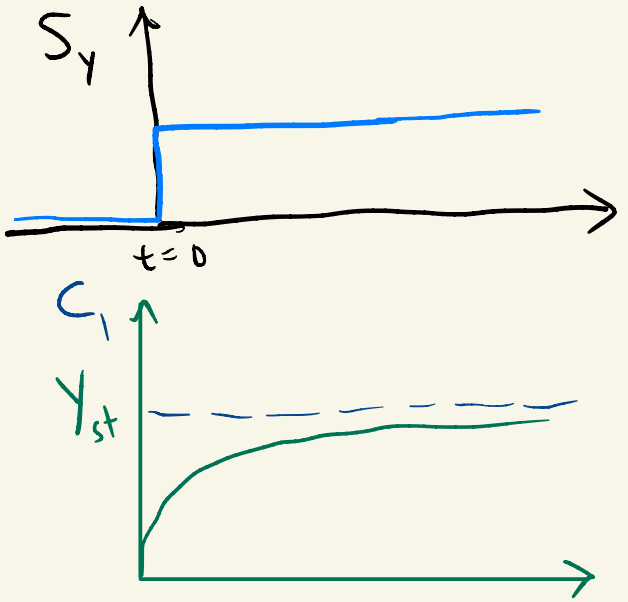
0

What is the time dependence of concentration of protein Y after induction at time $t = 0$?

Simple regulation:

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

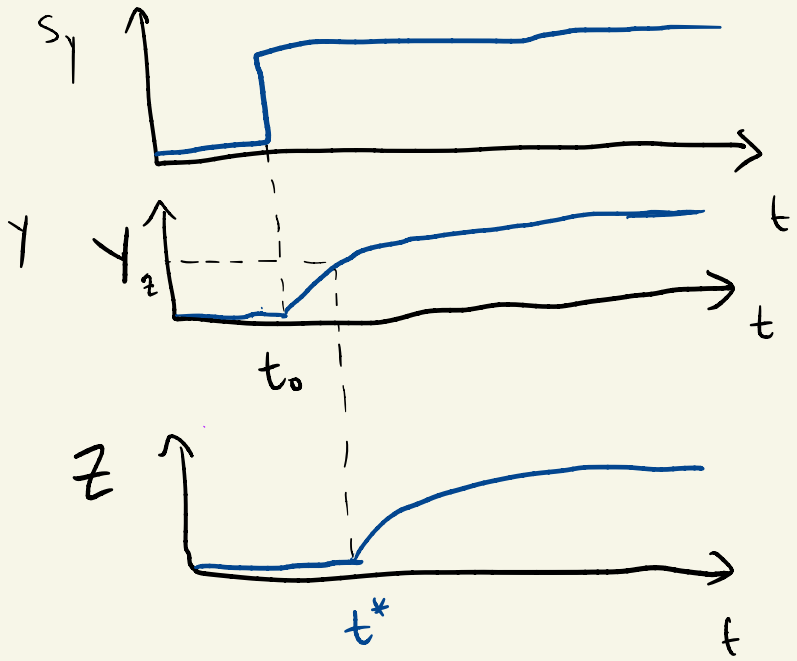
degradation production



$$Y = Y_{st}\left(1 - e^{-\alpha t}\right) \quad ; \quad Y_{st} = \beta/\alpha$$

Suppose gene Z requires a concentration $Y = Y_z$ to be activated.

What is $Z(t)$?



"Cascade", delay in protein production

$$Y(t^*) = Y_z$$

$$t^* - t_0 = ?$$

Course overview