Introduction to mathematical modelling with ODEs

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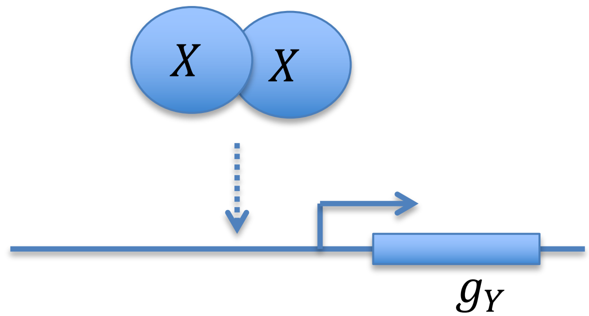
4. Gene regulation

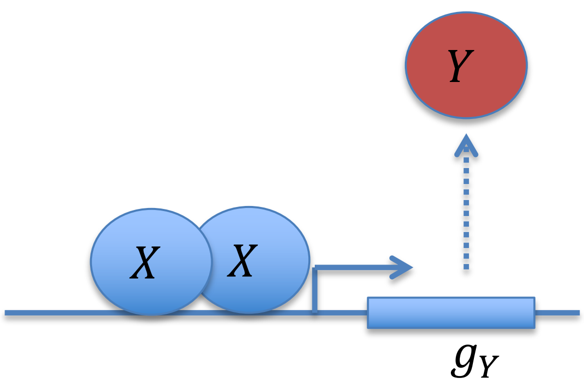
What is true for E. coli is also true for the elephant.
Jacques Monod

Gene regulation

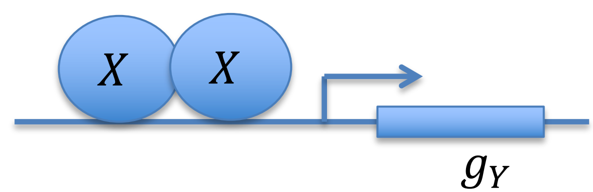
Transcription factor X
Gene g_Y
Protein Y



Here cooperativity
$n = 2$



Activation

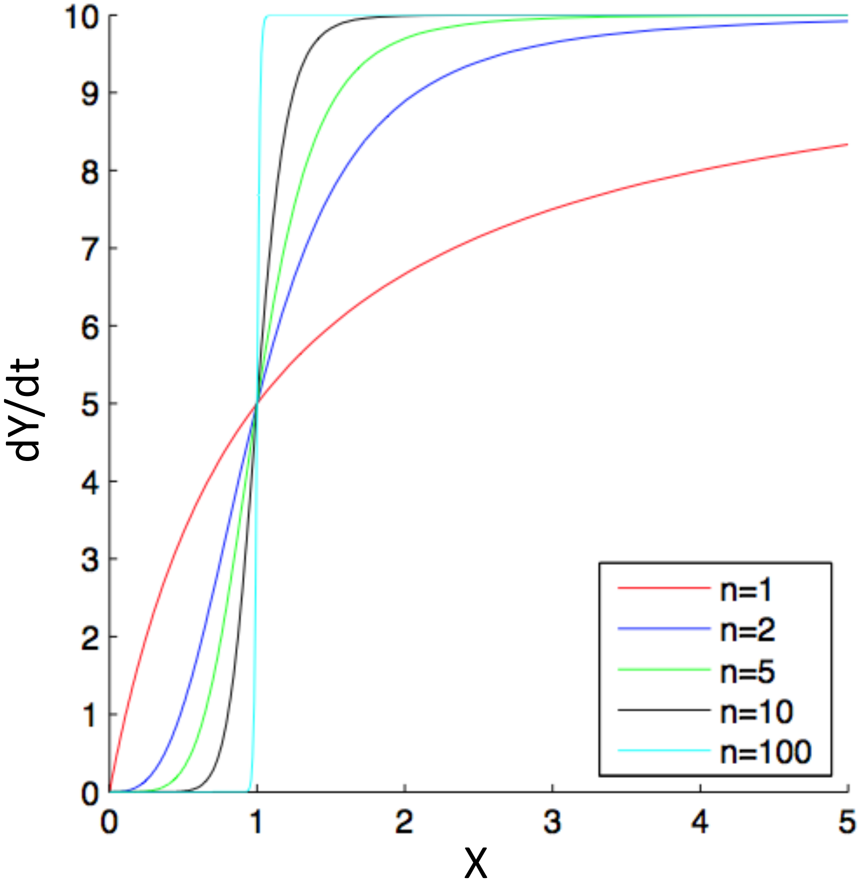


Repression

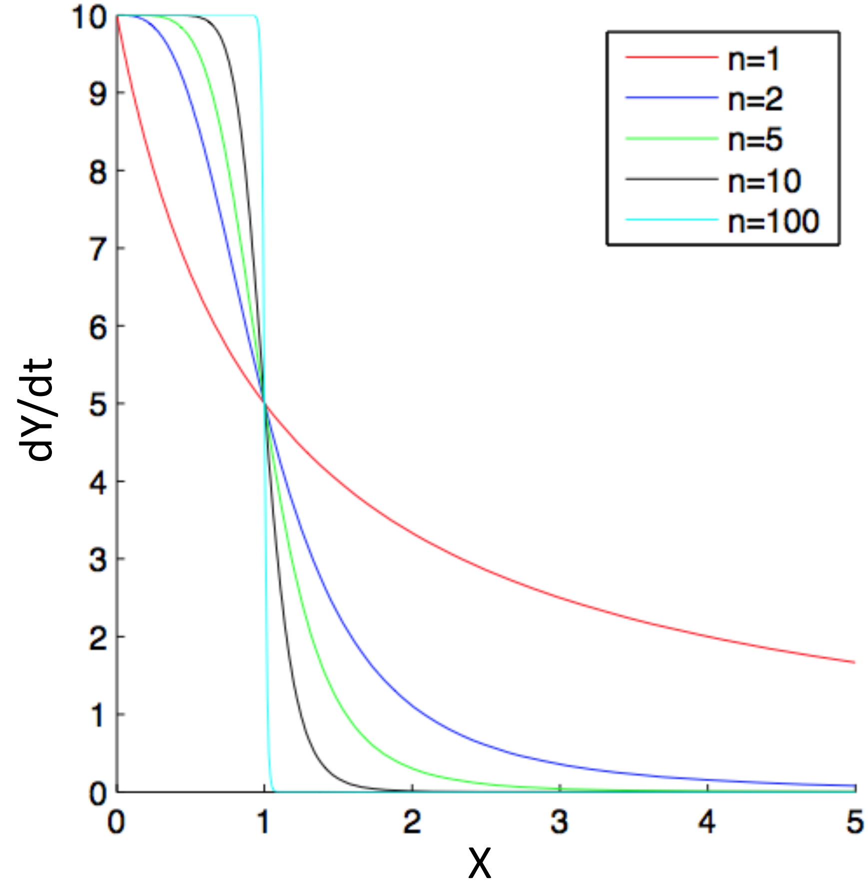
Regulation: Hill functions

Increased cooperativity steepens the response

Activation



Repression



Deriving Hill functions

- For simplicity, combine transcription and translation

- If X is activating, what is the rate of production of Y?
- Recall the enzymatic system and Michalis-Menten equation.
- This assumes binding/unbinding of Y to promoter is fast

$$g_Y + nX \rightleftharpoons g_Y.X_n \rightarrow g_Y + Y$$

$$\frac{dY}{dt} = \frac{kX^n}{K^n + X^n}$$

- n is the cooperativity (number of activator molecules required to activate)

An alternative viewpoint

- We can think about our model in the following way

- Probability that the transcription factor is bound is given by the Hill function

$$P_{BOUND} = \frac{X^n}{K^n + X^n}$$

- Expression level is obtained by multiplying by strength k

$$\frac{dY}{dt} = \frac{kX^n}{K^n + X^n}$$

What about repression?

- In this case there is expression only if X is unbound
- What is the probability that X is unbound?

$$P_{BOUND} + P_{UNBOUND} = 1$$

$$P_{UNBOUND} = 1 - P_{BOUND}$$

$$P_{UNBOUND} = \frac{K^n}{K^n + X^n}$$

- Multiply by strength k

$$\frac{dY}{dt} = \frac{kK^n}{K^n + X^n}$$

Update our gene expression model

- Original gene expression model

$$\frac{dX}{dt} = a - bX$$

- Assuming a constant concentration of X
- Replace expression term a, with Hill functions
- Activation by X

$$\frac{dY}{dt} = \frac{kX^n}{K^n + X^n} - bY$$

- Repression by X

$$\frac{dY}{dt} = \frac{kK^n}{K^n + X^n} - bY$$

Update our gene expression model

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- Repression by X

$$\frac{dY}{dt} = \frac{kK^n}{K^n + X^n} - bY$$

What if X varies?

- Now assume that the transcription factor varies in time
- We now need a differential equation for X

- Assume that X increases at a constant rate, a, and it activates the production of Y

- We now have a system of differential equations

$$\frac{dY}{dt} = \frac{kX^n}{K^n + X^n} - bY$$

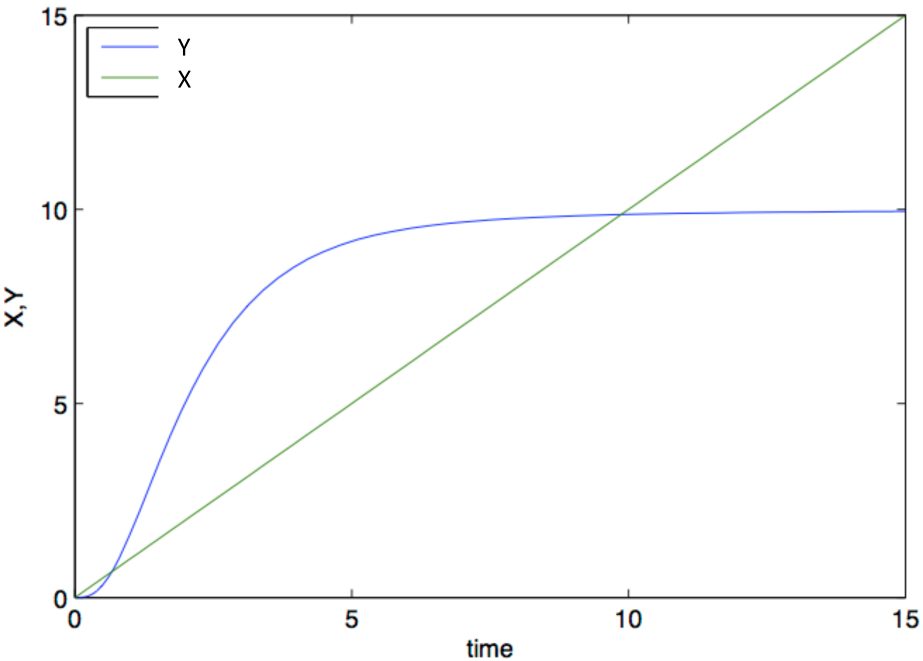
$$\frac{dX}{dt} = a$$

- This can't be solved analytically, so we integrate numerically

Linearly increasing activator

$$\frac{dY}{dt} = \frac{kX^n}{K^n + X^n} - \beta Y$$

$$\frac{dX}{dt} = a$$



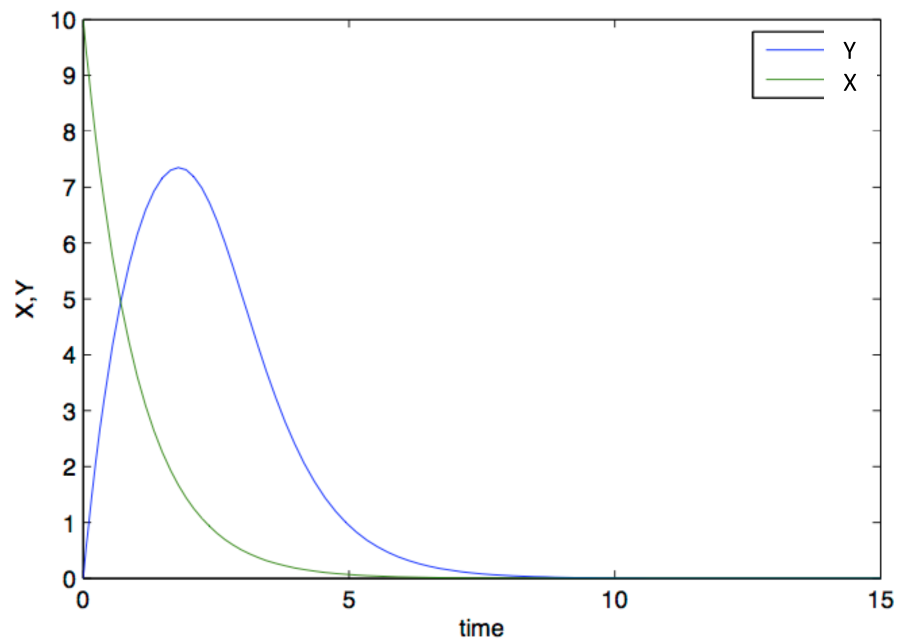
Protein expression is turned on, as expected

Exponentially decreasing activator

- Now we shall assume that the activator starts at a high level and decays exponentially

$$\frac{dY}{dt} = \frac{kX^n}{K^n + X^n} - \beta Y$$

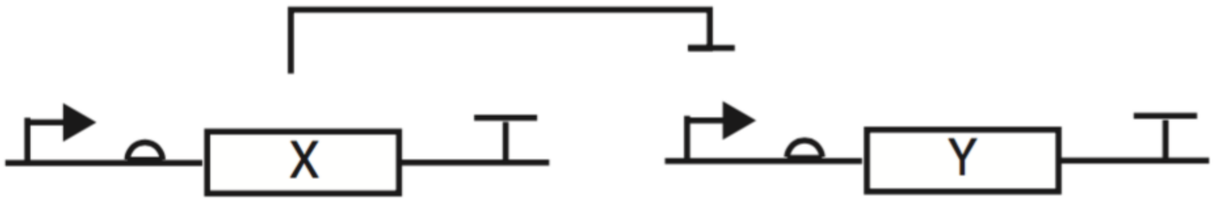
$$\frac{dX}{dt} = -bX$$



- Very different behaviour! (cf stress response, transcription bursts)

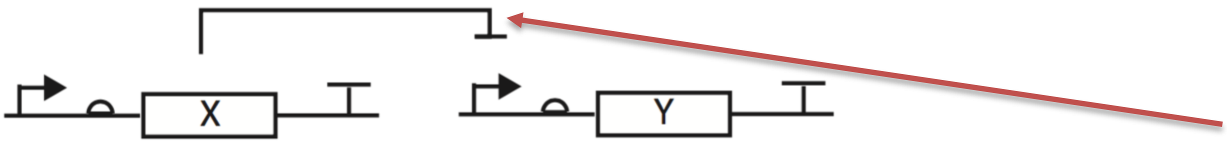
Task 4.1

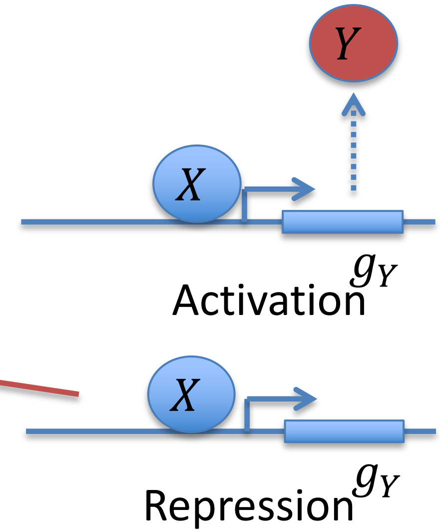
- Can you write down some reactions that model this genetic circuit in a bacterial cell:



- Can you do this for two abstractions:
  - Protein level
  - Protein + RNA level

Task 4.1: answer (1)



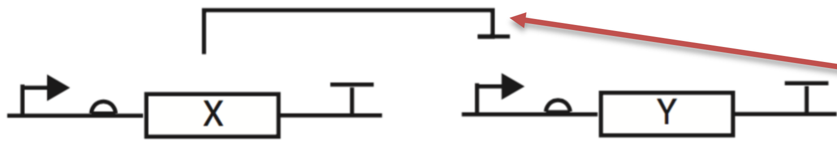


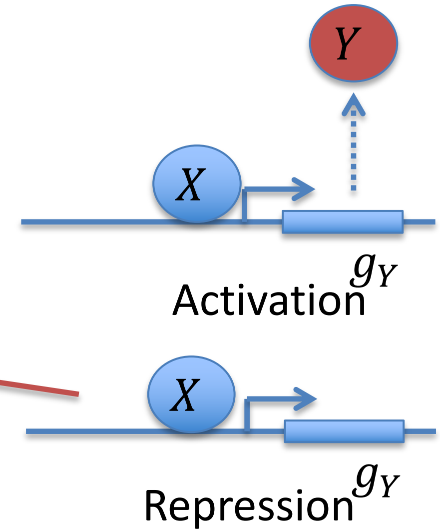
- Considering protein level

$$g_X \rightarrow g_X + X \qquad X + g_Y \rightarrow X g_Y \qquad g_Y \rightarrow g_Y + Y$$

$$X \rightarrow \emptyset \qquad Y \rightarrow \emptyset$$

Task 4.1: answer (2)





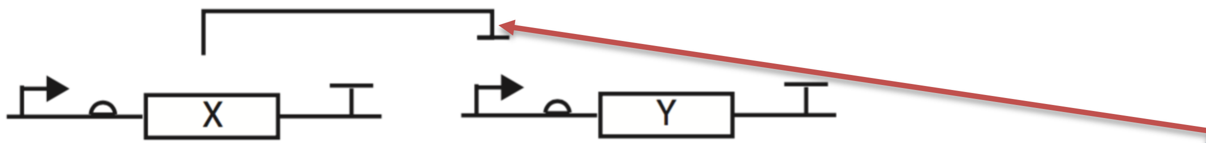
- Considering protein + RNA level

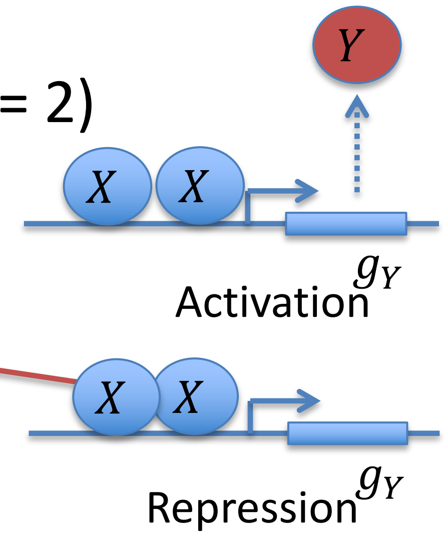
$$g_X \rightarrow g_X + X_{rna} \qquad g_Y \rightarrow g_Y + Y_{rna} \qquad X + g_Y \rightarrow Xg_Y \qquad X \rightarrow \emptyset$$

$$X_{rna} \rightarrow X \qquad Y_{rna} \rightarrow Y \qquad Y \rightarrow \emptyset$$

Task 4.2

- Write a model for this system (cooperativity = 2)





  - First decide on the level of abstraction (mRNA, protein)
  - Write down the reactions
  - Write down the differential equations

Task 4.2: answer

- Write down the reactions (protein level only)

$g_X \to g_X + X$ $\quad X + g_Y \to Xg_Y$ $\quad g_Y \to g_Y + Y$

$X \to \emptyset$ $\quad$ Y → Ø

- Write down the differential equations:
  - First input-output for each species, where a, α are the expression rates of X and Y and b, β are the degradation rates of X and Y respectively

$$\frac{dX}{dt} = a - bX \qquad \frac{dY}{dt} = \alpha - \beta Y$$

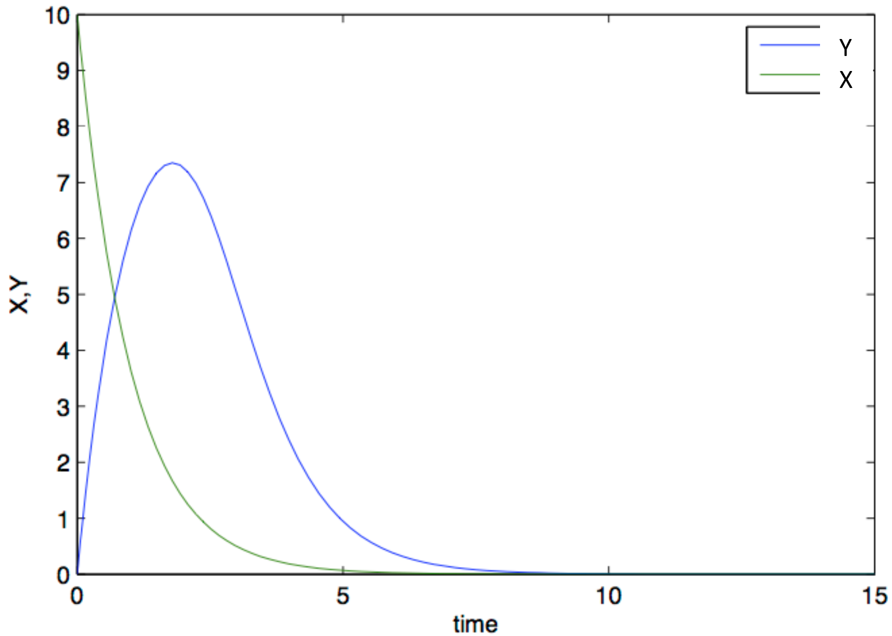
  - Replace α with a Hill function for repression by X with $n = 2$ for the cooperativity:

$$\frac{dX}{dt} = a - bX \qquad \frac{dY}{dt} = \frac{kK^2}{K^2 + X^2} - \beta Y$$

Task 4.3

$$\frac{dY}{dt} = \frac{kX^n}{K^n + X^n} - \beta Y$$

$$\frac{dX}{dt} = -bX$$



- Reason how the pulse like behaviour emerges from the interaction of the transcription factor, the promoter and the transcription of X

Task 4.3: answer

- Reason how the pulse like behaviour emerges from the interaction of the transcription factor, the promoter and the transcription of X

- X falls exponentially
- Initially activation is strong, rate of production of Y is high
- Eventually decay of Y balances the production
- Then decay dominates and we get exponential decay of Y