Introduction to mathematical modelling with ODEs

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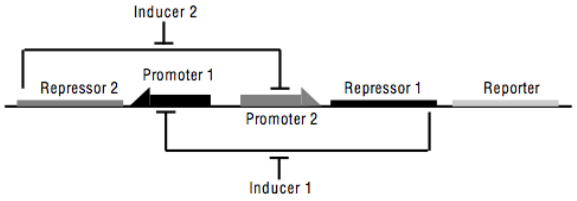
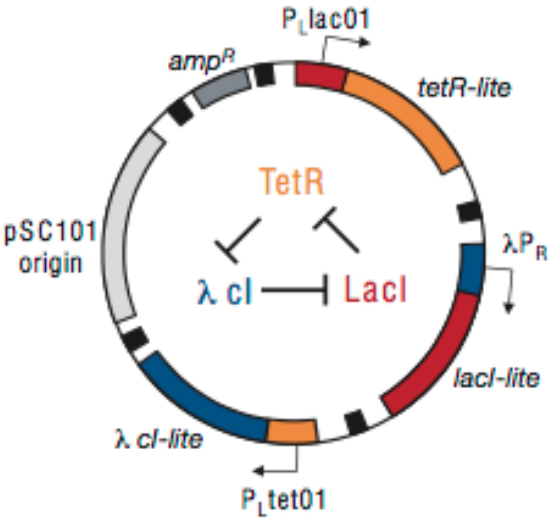
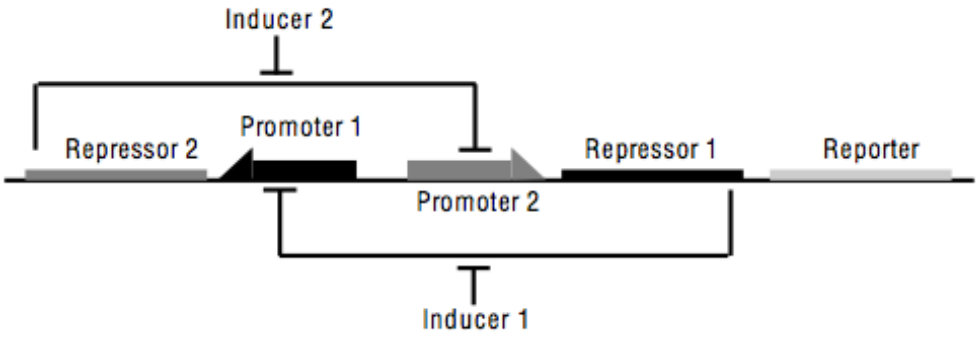
5. Gene regulatory networks

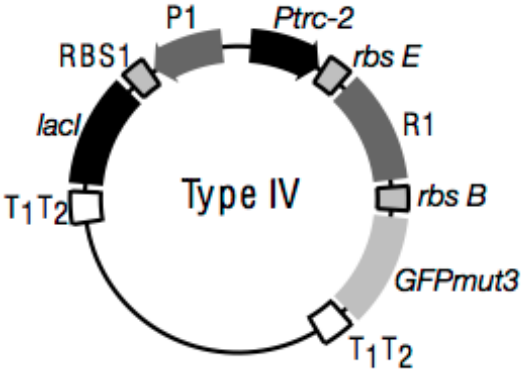


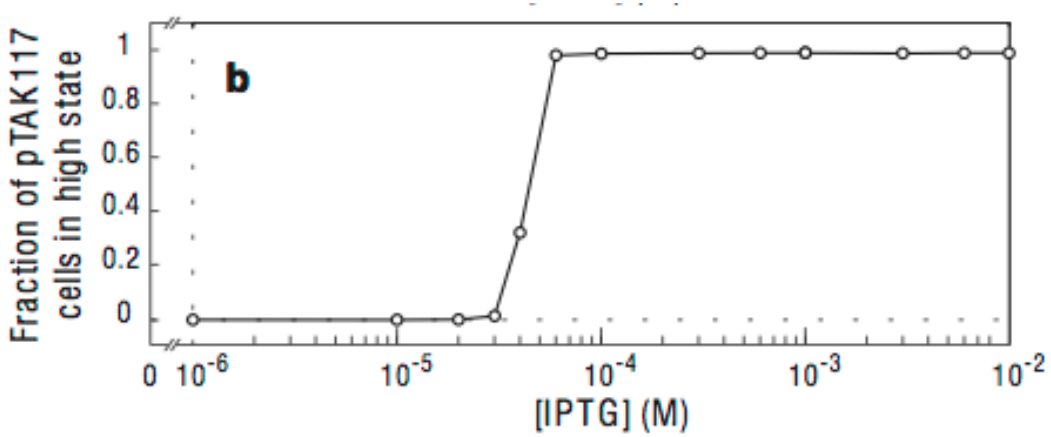


The toggle switch

- Cellular basis of memory and counting



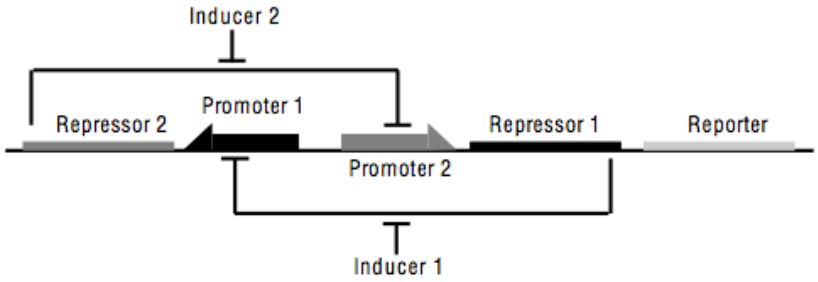




Construction of a genetic toggle switch in *Escherichia Coli*
Nature. 2000 Jan 20;403(6767):339-42.

Building the toggle model

- Two genes, g_U and g_V
- They produce proteins U and V
- U represses the production of V
- V represses the production of U



$$\frac{du}{dt} = \frac{k_u K_u^{n_v}}{K_u^{n_v} + v^{n_v}} - b_u u$$

$$\frac{dv}{dt} = \frac{k_v K_v^{n_u}}{K_u^{n_u} + u^{n_u}} - b_v v$$

- Here k_u, k_v are the strengths
- n_u, n_v are the cooperativities

‘Toy’ models

- Often, we want to create a model that lacks details so that we can obtain insights from it
- We often simplify while keeping the essential properties
- Here assume the $K = 1$ and the $b = 1$

$$\frac{du}{dt} = \frac{k_u}{1 + v^{n_v}} - u$$

$$\frac{dv}{dt} = \frac{k_v}{1 + u^{n_u}} - v$$

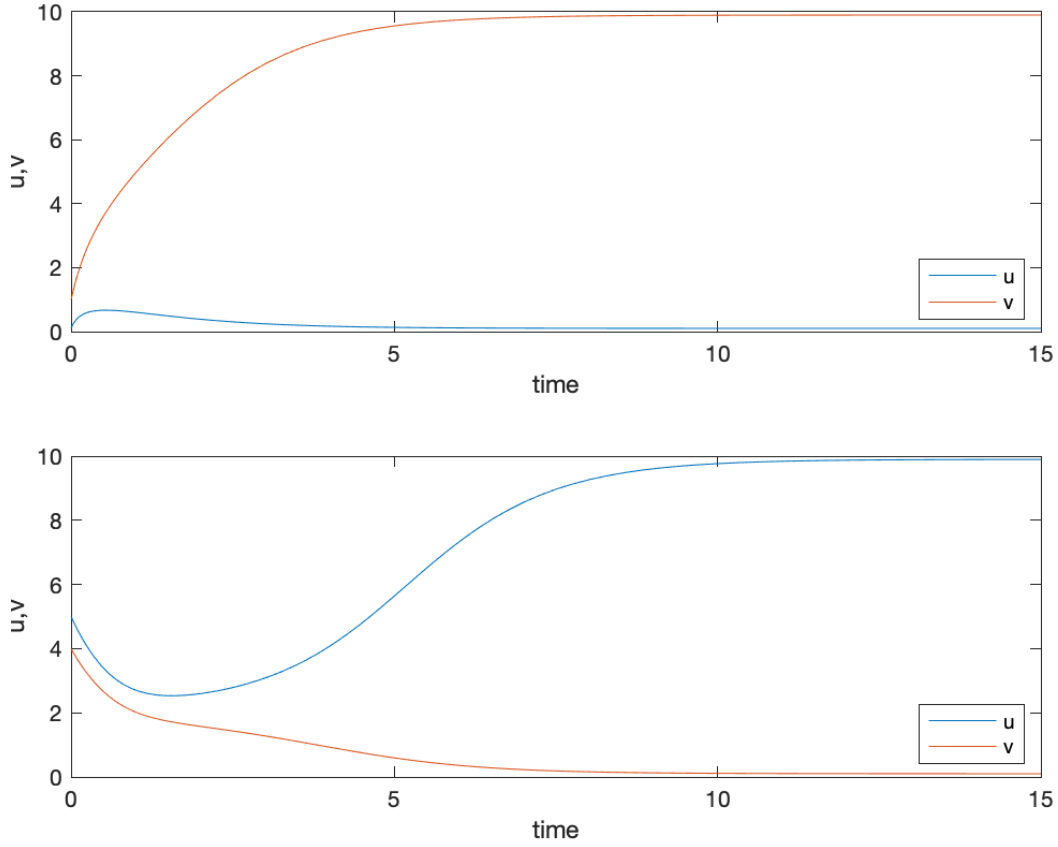
Task 5.1

- Can you write down the reactions and derive the toggle switch system equations

$$\frac{du}{dt} = \frac{k_u}{1 + v^{n_v}} - u$$

$$\frac{dv}{dt} = \frac{k_v}{1 + u^{n_u}} - v$$

Numerical results



Note that depending on the initial conditions the system ends with u high OR v high

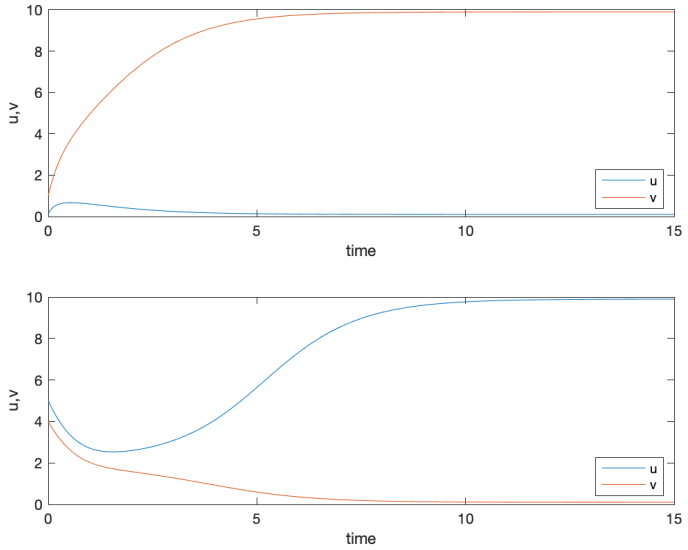
Dynamical systems terminology (1)

- A **phase space** of a dynamical system is a space in which all possible states of the system are represented. Phase spaces for systems like the toggle switch that have two variables can be visualized on a 2D plot

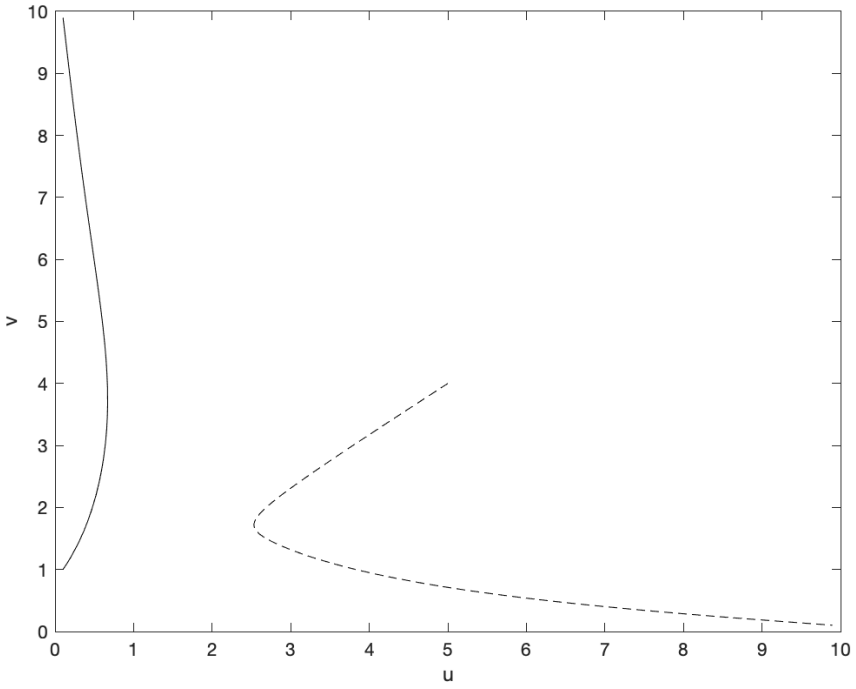
Phase space for toggle

- We plot the phase space
- In this case it is two dimensional as we have two variables u and v.
- Note that time is not on either axis

Time course



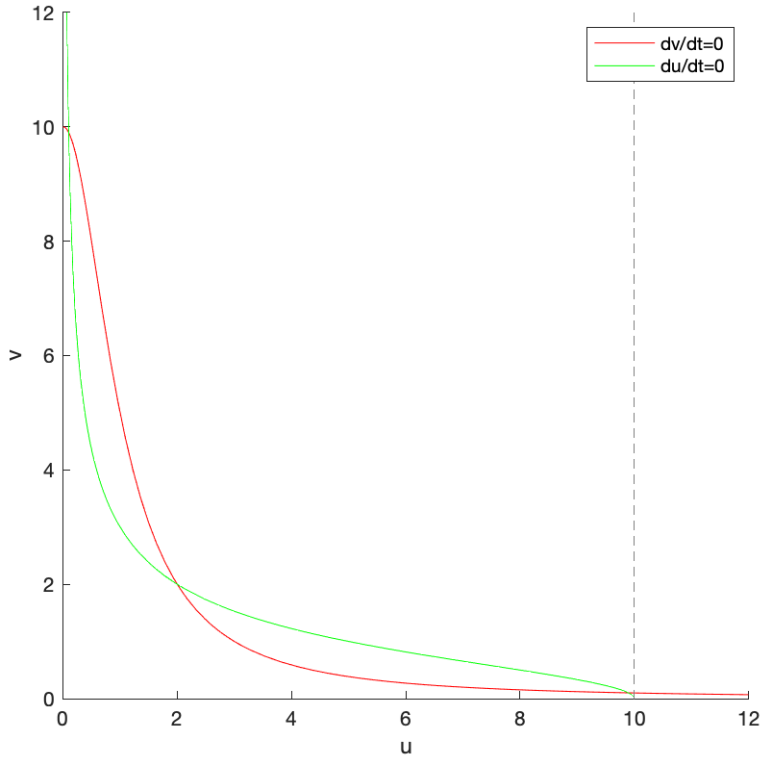
Phase space



Dynamical systems terminology (2)

- A **nullcline** is the set of points in phase space where the time derivative of one of the system variables is 0. In the toggle there are two:

$$\frac{du}{dt} = 0 \quad , \quad \frac{dv}{dt} = 0$$



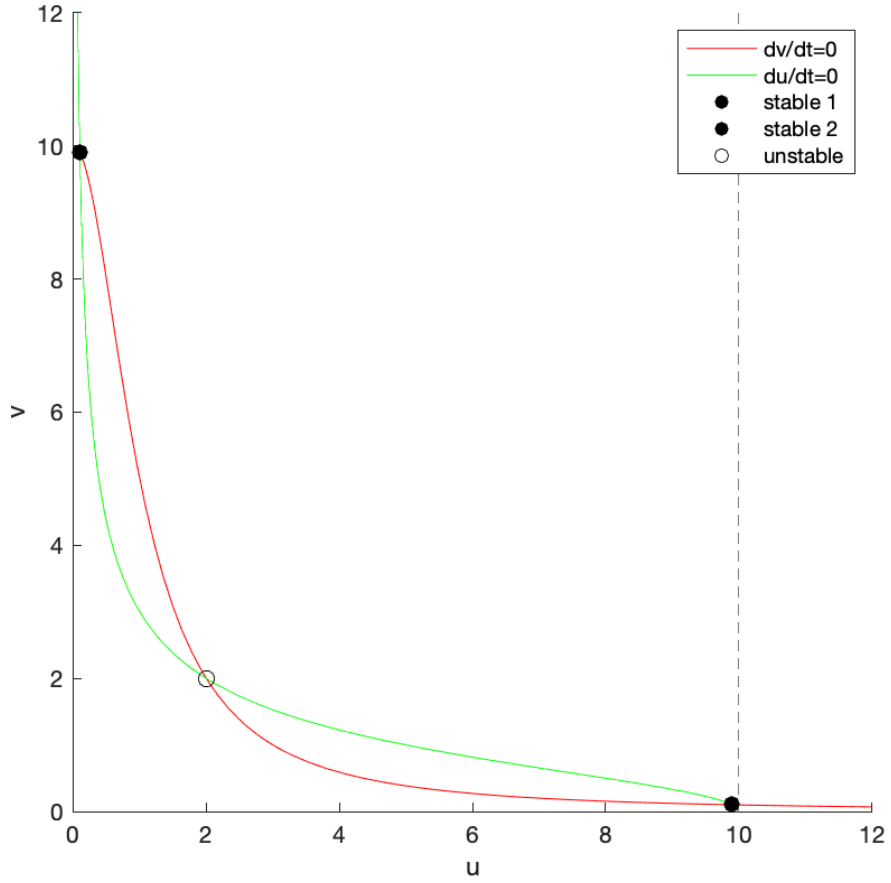
Dynamical systems terminology (3)

- A **steady state** is a point in phase space for which the time derivatives of all system variables are 0. In other words a point at which all nullclines intersect.

$$\frac{du}{dt} = 0 \text{ and } \frac{dv}{dt} = 0$$

- **Stable steady state** : the system will return to the steady state after small perturbations or
- **Unstable steady state** : the system will diverge after small perturbations

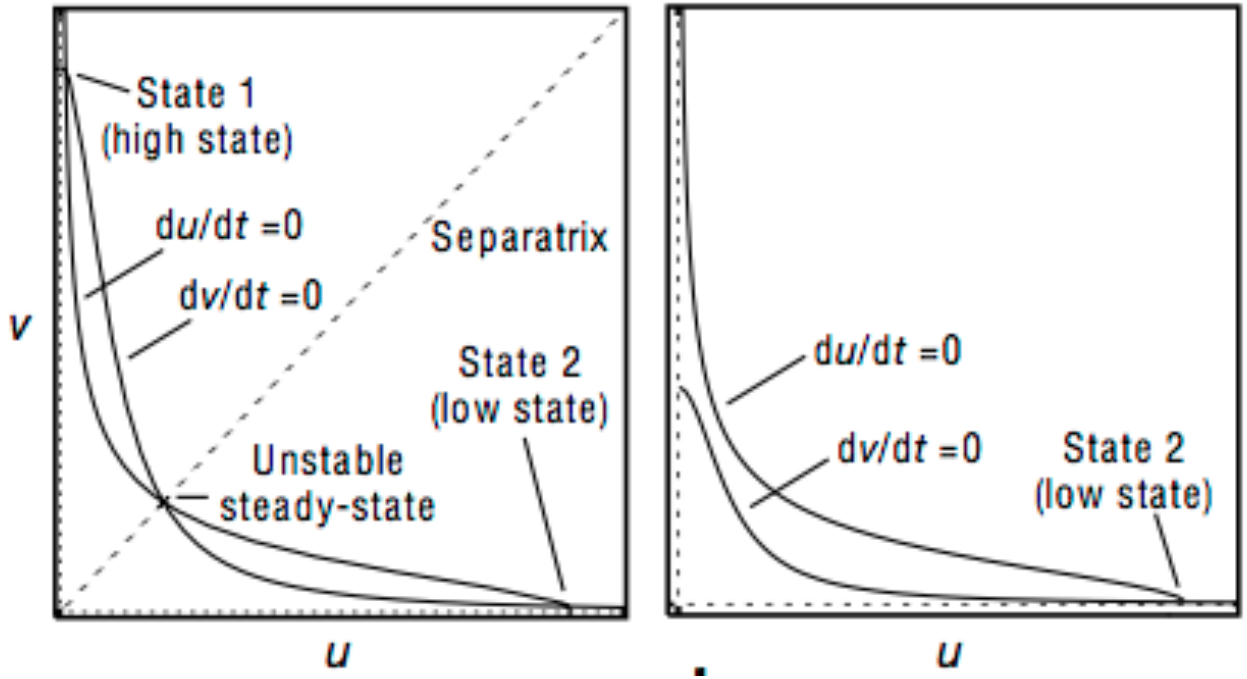
Steady states for toggle switch



The two stable steady states are what give the system memory and switching

Bistability

- The system can be toggled between two stable steady states (high state and low state) by two inducers, this is a bistable system.



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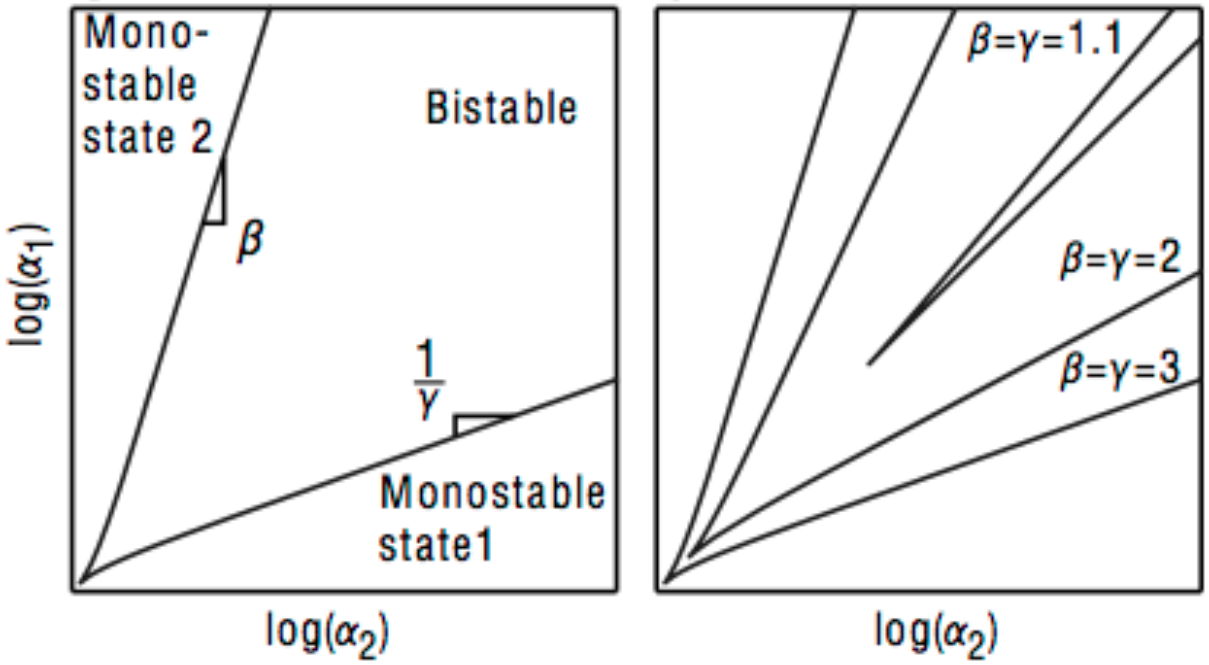
Bistable regions

Bistability depends on the system parameters, here the two alpha values. If we want a functioning toggle switch, we must stay within the bistable region.



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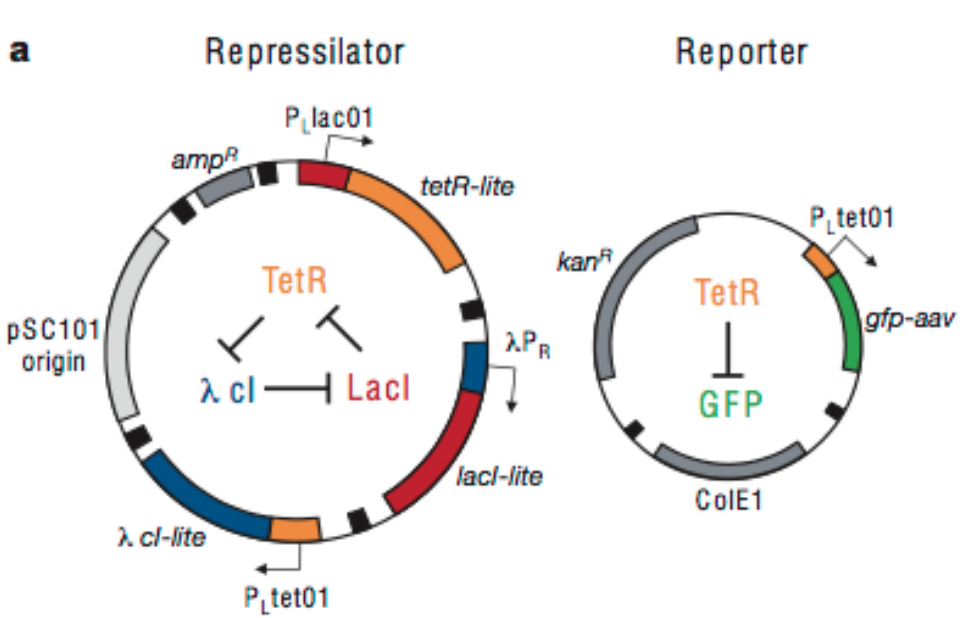
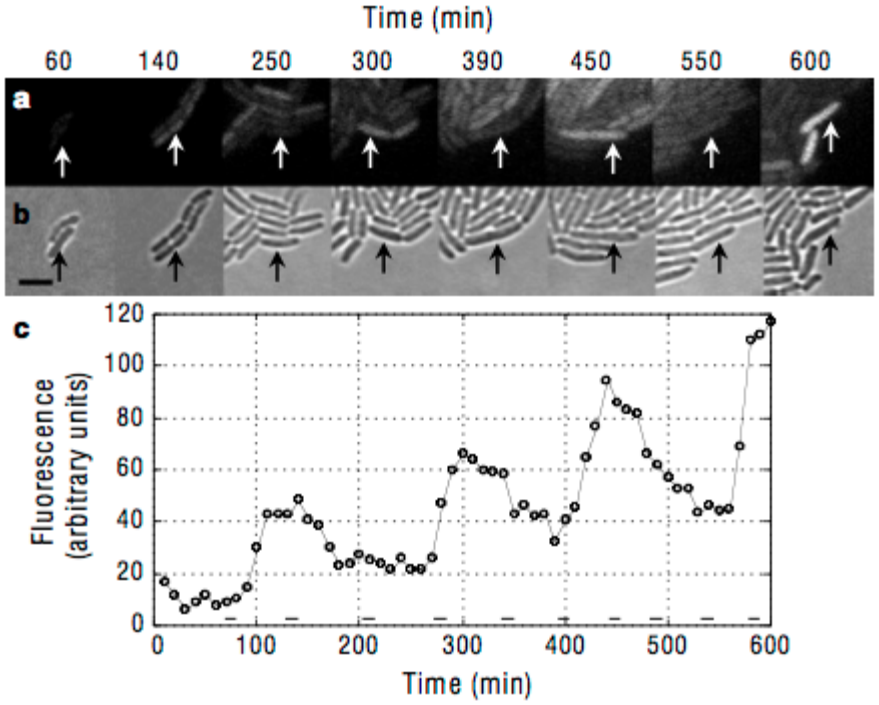
This kind of analysis can be used when designing synthetic systems e.g. which genetic parts should I use to achieve bistable behavior?

The repressilator

- An oscillator based on the cyclic negative feedback of three components





A synthetic oscillatory network of transcriptional regulators
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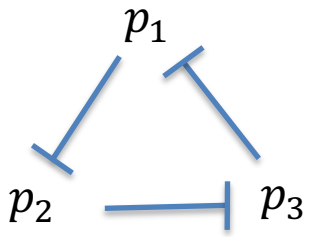
The repressilator

The full model

$$\frac{dm_1}{dt} = -m_1 + \frac{k}{1+p_3^n} + k_0 \qquad \frac{dp_1}{dt} = -\beta(p_1 - m_1)$$

$$\frac{dm_2}{dt} = -m_2 + \frac{k}{1+p_1^n} + k_0 \qquad \frac{dp_2}{dt} = -\beta(p_2 - m_2)$$

$$\frac{dm_3}{dt} = -m_3 + \frac{k}{1+p_2^n} + k_0 \qquad \frac{dp_3}{dt} = -\beta(p_3 - m_3)$$



Assumptions

Symmetrical parameters

Protein decay is equal to mRNA production rate

Variables

m_1, m_2, m_3 are the mRNAs

p_1, p_2, p_3 are the proteins

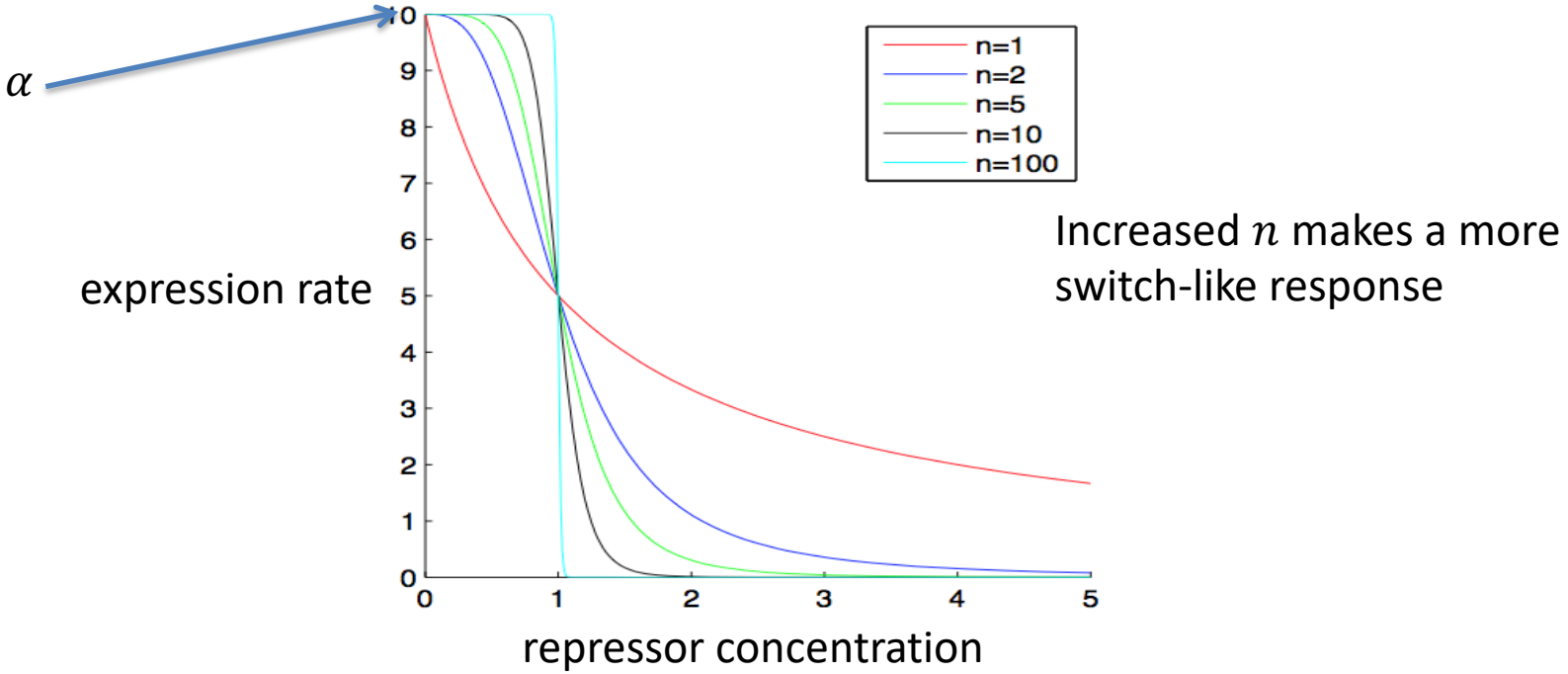
Free parameters

k_0, k, n, β

The parameters

- k_0 is basal gene expression rate
  - expression of each gene when there is no repression
- β is protein decay (and mRNA production rate constant)

- k is maximal transcription rate
- n is cooperativity of repressors ($n = 1$ monomer, $n = 2$ dimer, $n = 3$ trimer…)



Increased n makes a more switch-like response

Task 5.2

- Can you write down the reactions and derive the repressilator system equations

$$\frac{dm_1}{dt} = -m_1 + \frac{k}{1+p_3^n} + k_0 \qquad \frac{dp_1}{dt} = -\beta(p_1 - m_1)$$

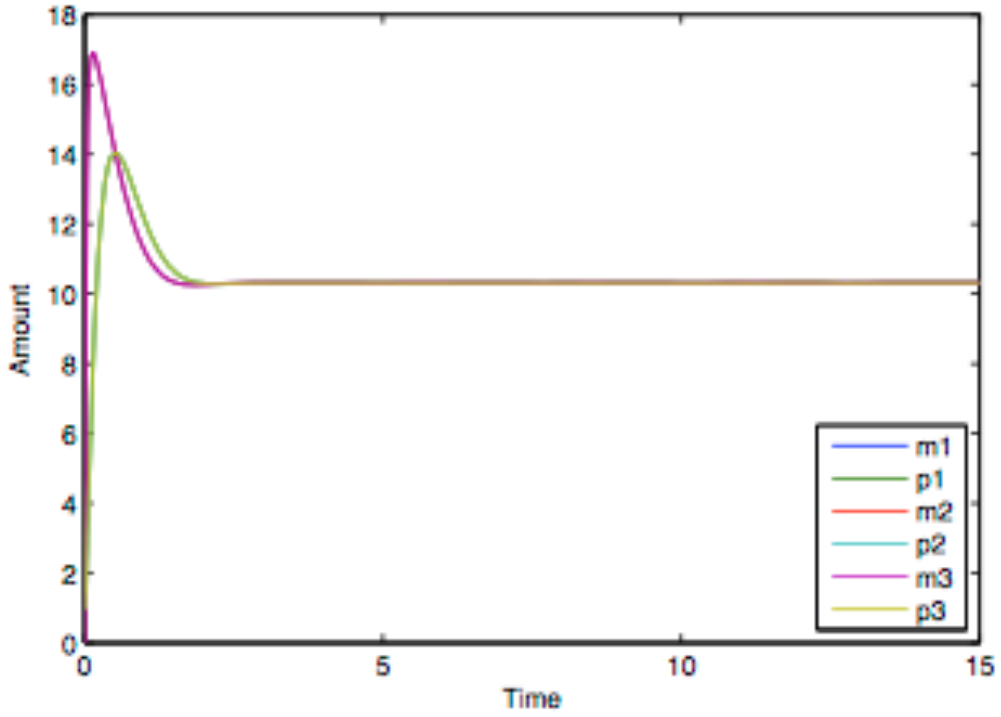
$$\frac{dm_2}{dt} = -m_2 + \frac{k}{1+p_1^n} + k_0 \qquad \frac{dp_2}{dt} = -\beta(p_2 - m_2)$$

$$\frac{dm_3}{dt} = -m_3 + \frac{k}{1+p_2^n} + k_0 \qquad \frac{dp_3}{dt} = -\beta(p_3 - m_3)$$

Stable steady state

parameters: $k_0 = 1, n = 2, \beta = 5, k = 1000$

initial conditions: $m_1, p_1, m_2, p_2, m_3, p_3 = 0,1,0,1,0,1$



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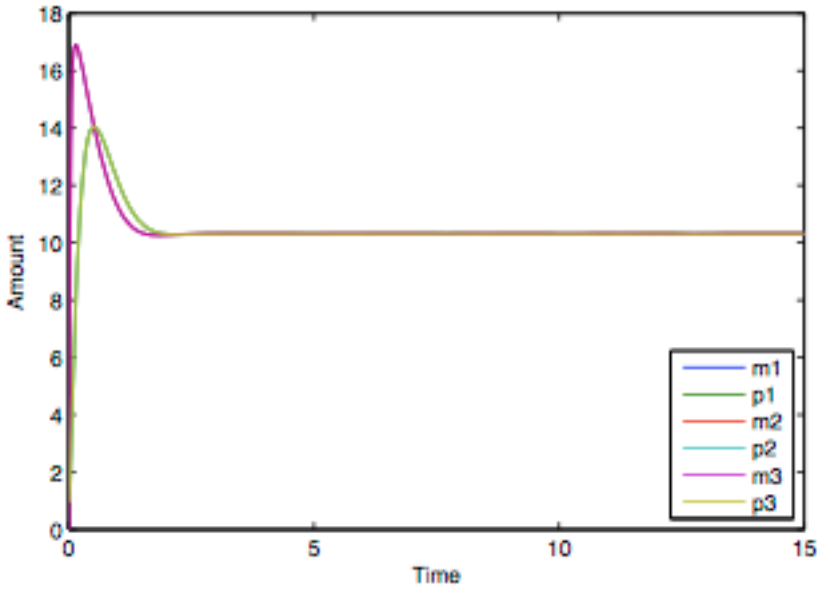
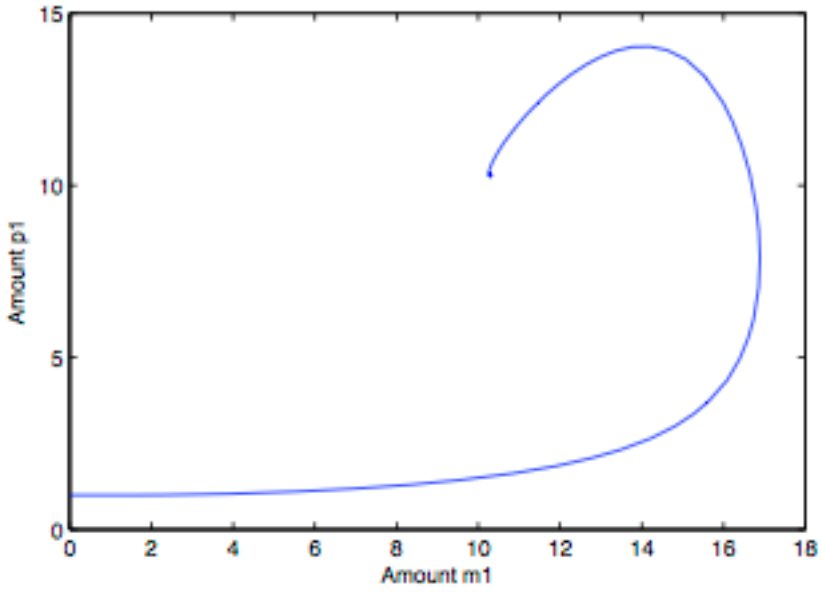


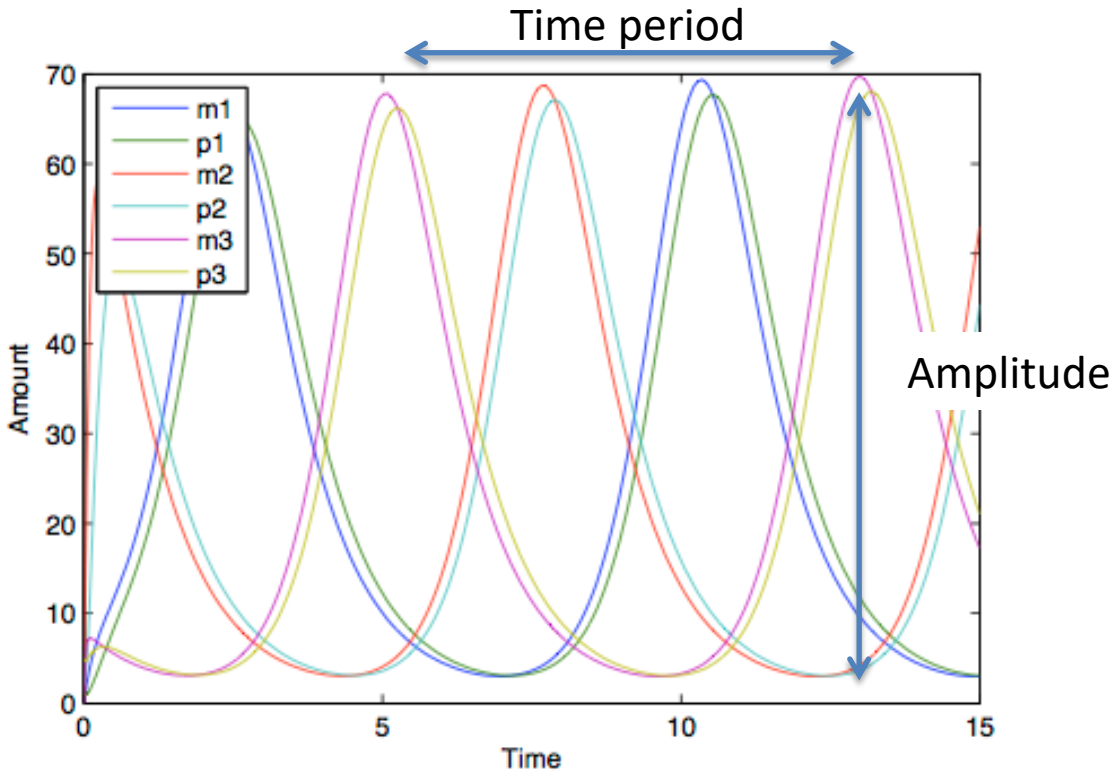


Stable spiral

Oscillations

parameters: $k_0 = 1, n = 2, \beta = 5, k = 1000$

initial conditions: $m_1, p_1, m_2, p_2, m_3, p_3 = 0,1,0,2,0,5$



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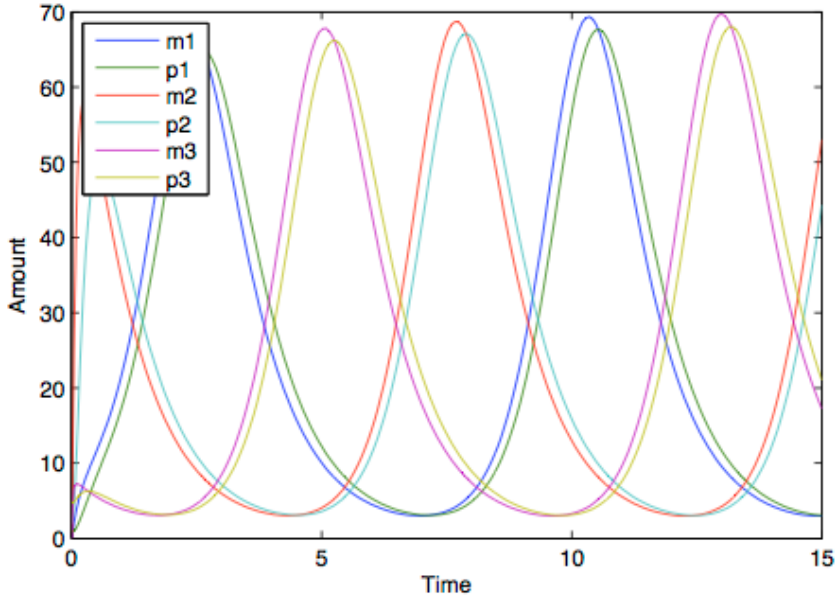
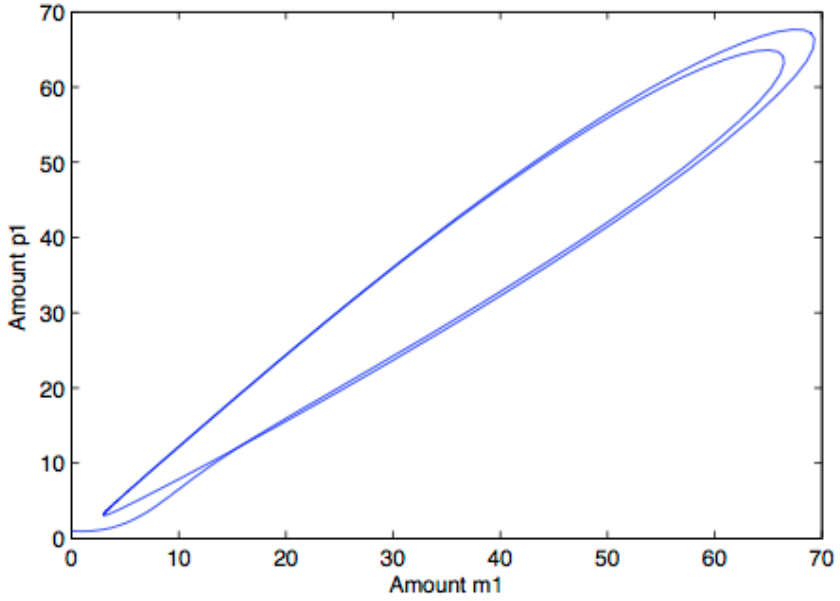
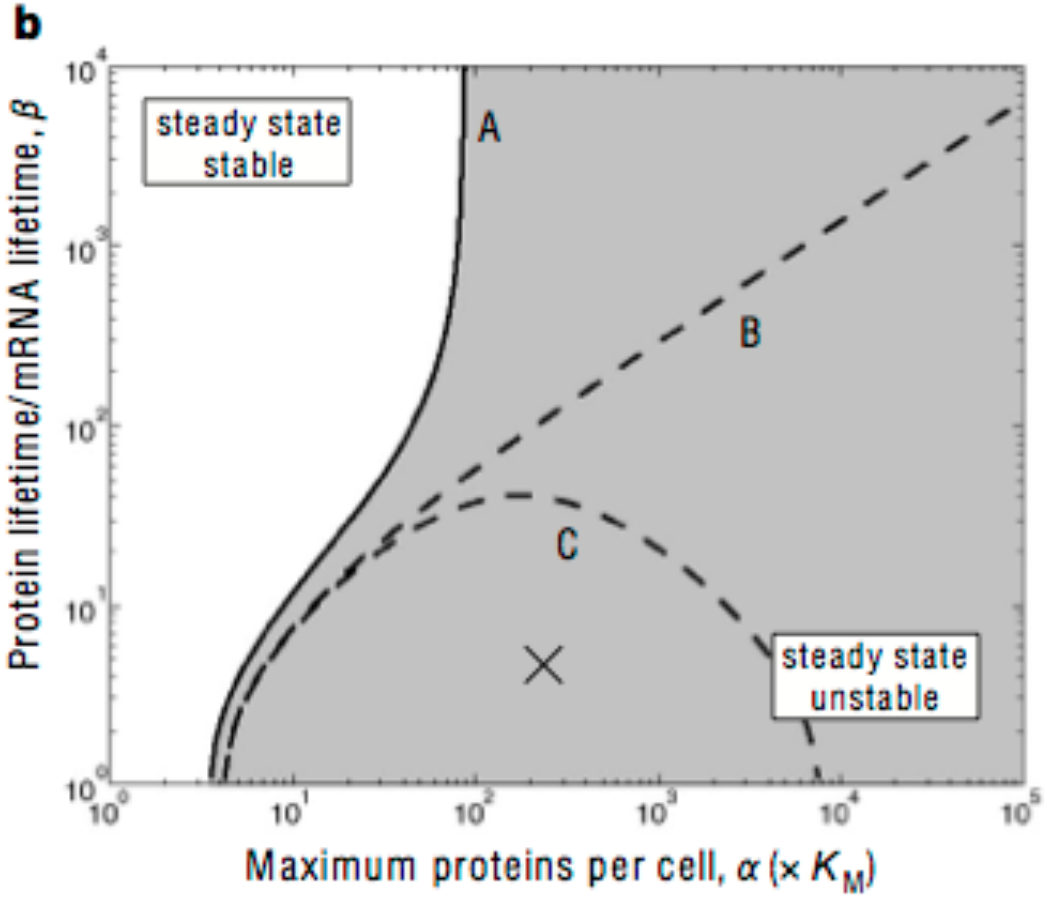




Limit cycle

Making predictions



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Summary of the session

- We can build simple models of cell processes that are useful for our understanding of existing systems and for building novel systems
- Performing analysis *in silico* is much easier than *in vivo*
- We often find behaviour that is surprising or hard to predict without the mathematical model
- Writing a mathematical model is way to formalise our understanding of a system. It can be tested and refined!