RNA Velocity: a mathematical model to predict cellular differentiations

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Comprehensible Seminars – Institute of Mathematics, ULiège

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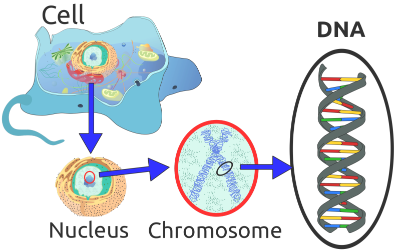
Deoxyribonucleic acid (DNA)



([5])

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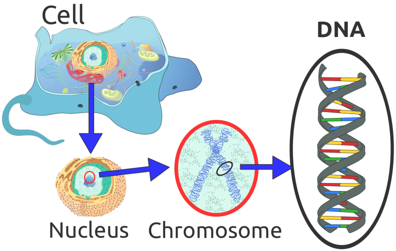

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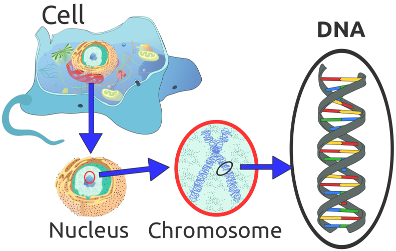

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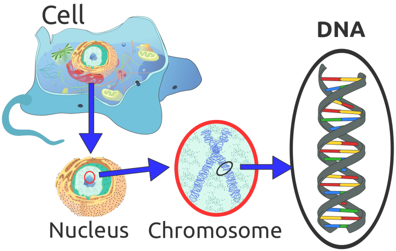

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- Structure:
  - Double-helix (2 strands, with links A-T or C-G)
  - Folded to form *Chromosomes* (23 pairs for human beings)

Genes and ribonucleic acid (RNA)

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- Ribonucleic Acid (RNA): 4 nucleotides (A,C,G, and *Uracil* (U)), with ribose as sugar (usually, one simple strand)

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Coding genes and mRNA

- Among genes, there exist *coding genes*: they produce *messenger RNA* (mRNA), which is used to build some proteins needed by the organism
- Other genes are called *RNA genes*

Purpose

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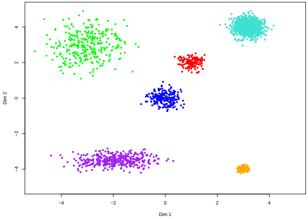

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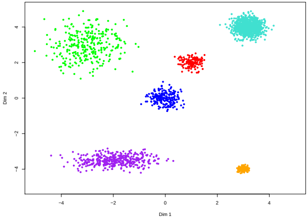

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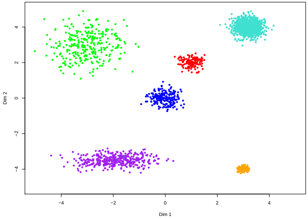

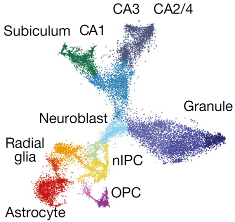

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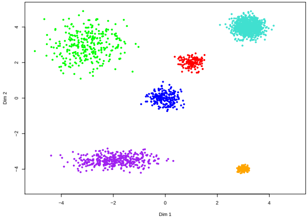

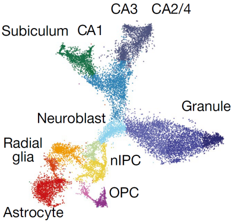

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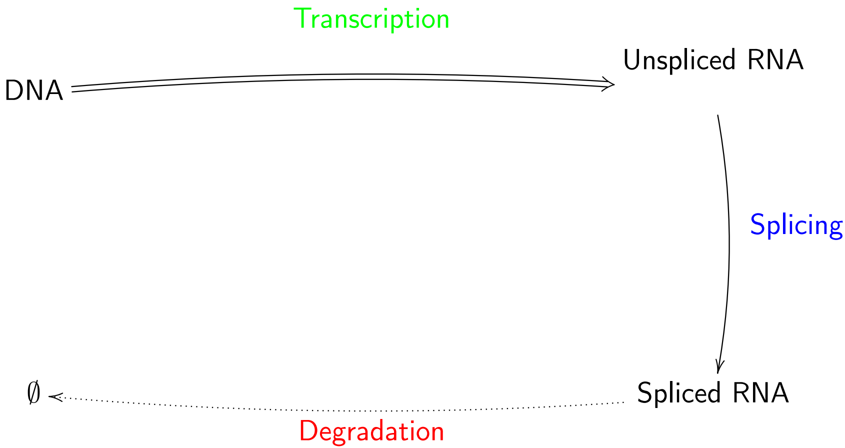
- Purpose: **modelling this differentiation by study "RNA dynamics"** (transcription + splicing)

RNA dynamics

In **one cell**, for **one gene** ([1])...



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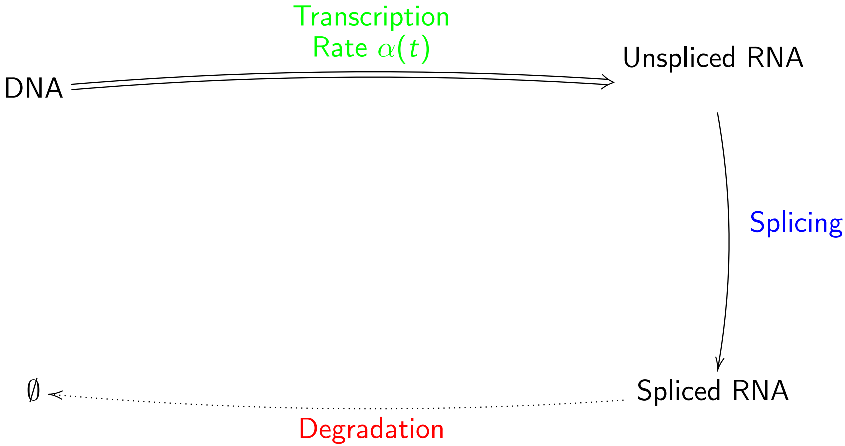

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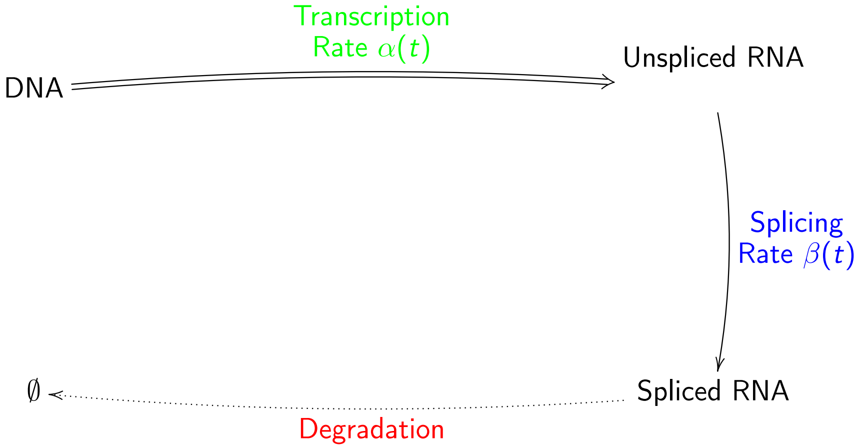

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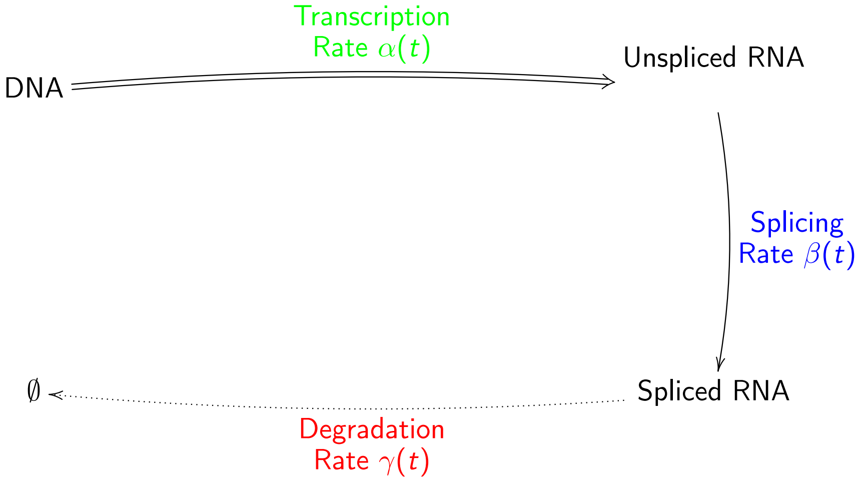

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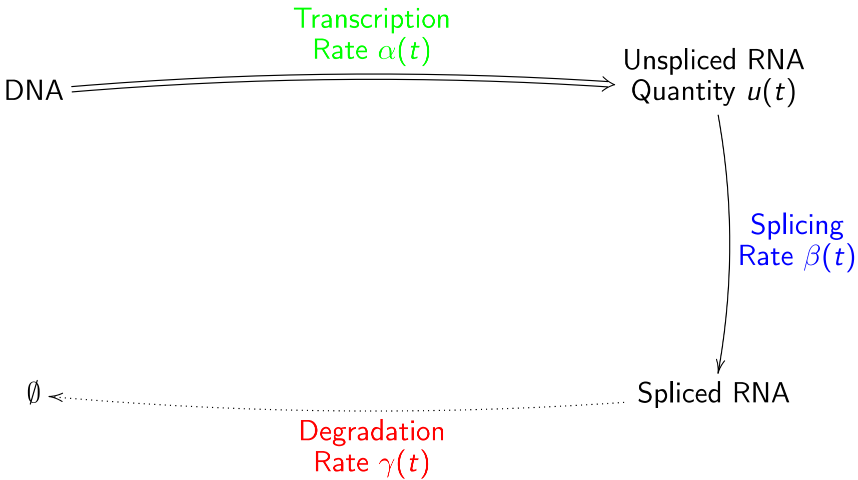

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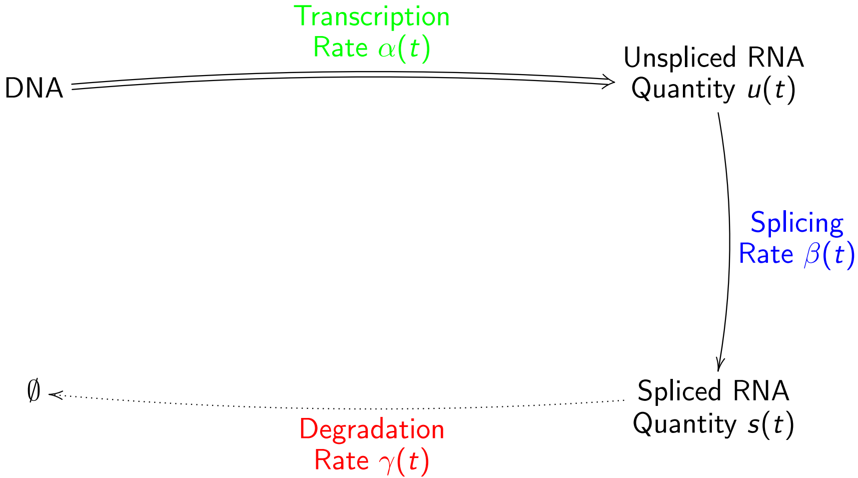

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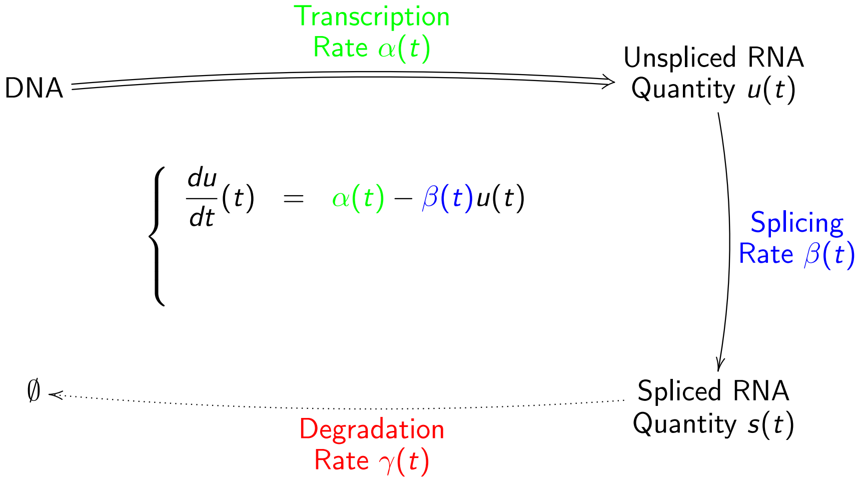

$$\left\{ \frac{du}{dt}(t) = \alpha(t) - \beta(t)u(t) \right.$$

RNA dynamics

In **<u>one</u> cell**, for **<u>one</u> gene** ([1])...

Transcription
Rate $\alpha(t)$

DNA ⟹ Unspliced RNA
Quantity $u(t)$

$$\begin{cases} \frac{du}{dt}(t) & = & \alpha(t) - \beta(t)u(t) \\ \frac{ds}{dt}(t) & = & \beta(t)u(t) - \gamma(t)s(t) \end{cases}$$

Splicing
Rate $\beta(t)$

Spliced RNA
Quantity $s(t)$

$\emptyset$

Degradation
Rate $\gamma(t)$

Remarks

1. Parameters
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$$\alpha \geq 0, \qquad \beta > 0, \qquad \gamma > 0$$

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   - $u(t)$ and $s(t)$ are continuous functions describing integer numbers: **expected values**!

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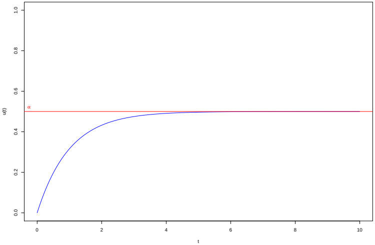
2. Distribution
    - $u(t)$ and $s(t)$ are continuous functions describing integer numbers: **expected values**!
    - **Real** integer values: (asymptotic) 2-dimensional Poisson distribution

Solution of the first equation

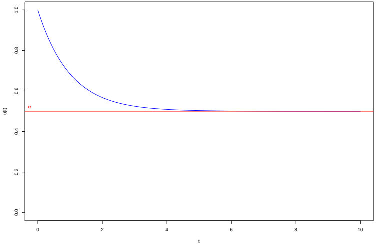
If $u_0 := u(0)$,

$$u(t) = \alpha + (u_0 - \alpha)e^{-t}.$$

$u_0 < \alpha$



$u_0 > \alpha$



In all cases,

$$\lim_{t \to \infty} u(t) = \alpha.$$

Solution of the second equation

If $u_0 := u(0)$ and $s_0 := s(0)$,

$$s(t) = \begin{cases} \dfrac{\alpha}{\gamma} + \dfrac{u_0 - \alpha}{\gamma - 1} e^{-t} + \left(s_0 + \dfrac{\alpha - u_0}{\gamma - 1} - \dfrac{\alpha}{\gamma} \right) e^{-\gamma t} & \text{if} \quad \gamma \neq 1 \\ \alpha + \left[(u_0 - \alpha) t + s_0 - \alpha \right] e^{-t} & \text{if} \quad \gamma = 1 (= \beta). \end{cases}$$

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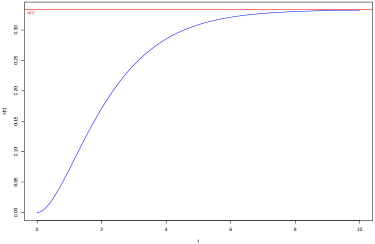
and so

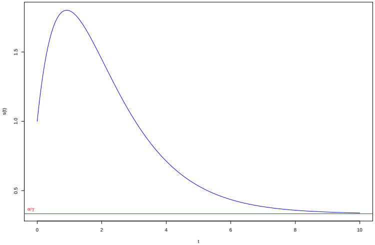
$$\boxed{\lim_{t \to \infty} \frac{u(t)}{s(t)} = \gamma.}$$

Solution of the second equation

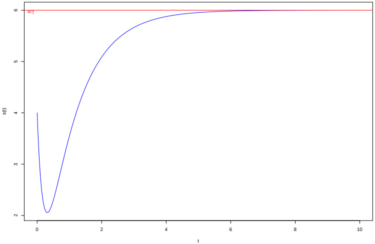
$u_0 = s_0 = 0, \ \alpha = 0.25, \ \gamma = 0.75$



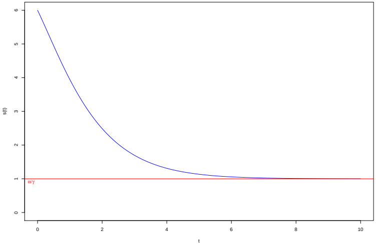
$u_0 = 3, \ s_0 = 1, \ \alpha = 0.25, \ \gamma = 0.75$



$u_0 = 3, \ s_0 = 4, \ \alpha = 30, \ \gamma = 5$



$u_0 = 4, \ s_0 = 6, \ \alpha = 1, \ \gamma = 1$



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In **one** **cell**, for p **genes**... ([1])

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  in a p-dimensional space (space of spliced quantities)

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Definition

The *RNA velocity* of the cell is

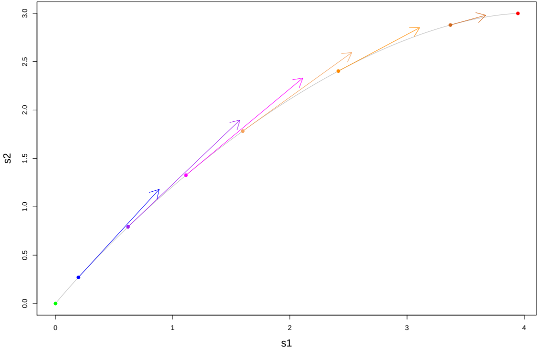
$$\vec{v} := \frac{d\vec{s}}{dt} = \left(\frac{ds_1}{dt}, \cdots, \frac{ds_p}{dt} \right).$$

Representations

Help for interpretation...

Example ($p = 2$)

$\alpha_1 = 2$, $\gamma_1 = 0.5$; $\alpha_2 = 3$, $\gamma_2 = 1$



- Grey curve: trajectory of the cell in the space of spliced quantities $(t \mapsto (s_1(t), s_2(t)))$
- Vectors: RNA velocities
- Red point: "steady" state

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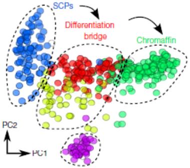
- Principle component analysis: quite natural, projection on P.C.;
- There exist some non-linear techniques (t-SNE ([4]), UMAP ([2])). Idea: arrows joining cells aligned along velocities...

Representations

Example: Schwann cell precursors (coming from [1])



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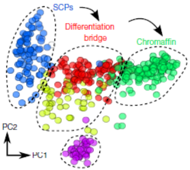
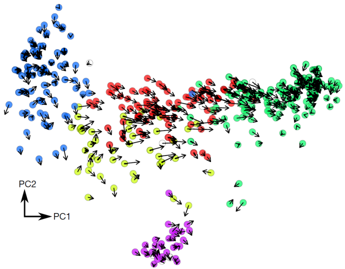
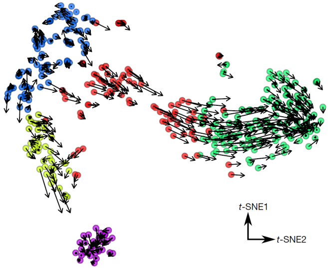


PCA



t-SNE



Estimation of γ

For <u>**one**</u> **fixed gene** and a given **sample of cells** (of size n)...

Assumption

Degradation coefficient γ depends **on the gene**, but <u>**not**</u> **on the cell**!

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How can we estimate the parameter γ associated to the fixed gene?

Phase portrait

- Reminder: in every cell, $\lim_{t\to\infty}(u(t)/s(t)) = \gamma$ so $u(t) \approx \gamma s(t)$ if $t \gg 0$.

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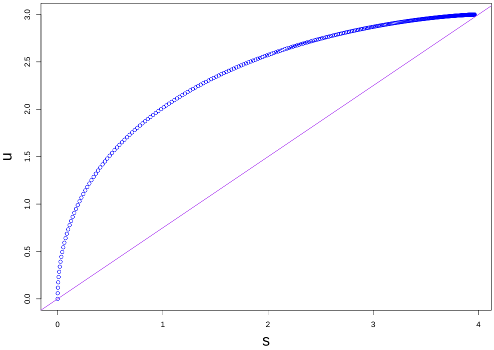
Theoritical example ($\alpha = 3,\ \gamma = 0.75$)

400 cells, uniformly generated in time



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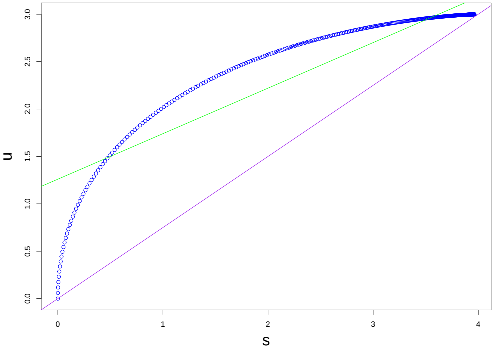

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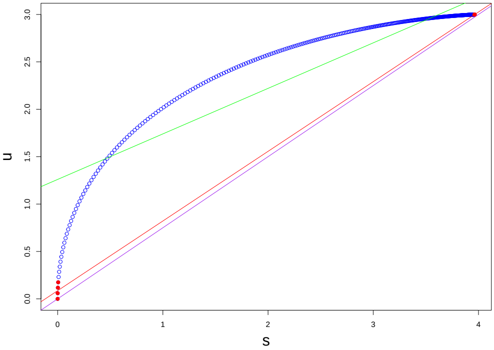

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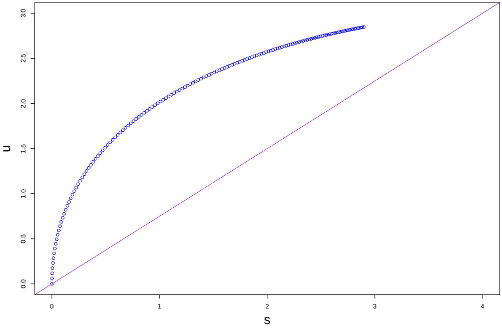
- Extreme-quantile linear regression (1%): $\gamma \approx 0.73493$

Estimation of γ: caution!

300 from the 400 previous cells...



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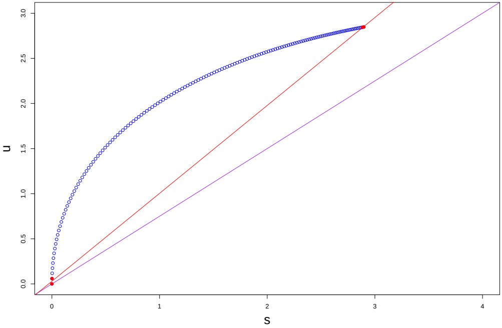

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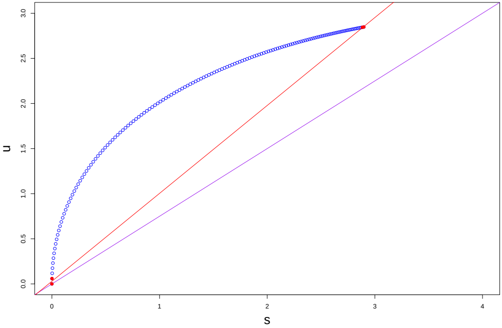

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Necessary condition: as many differentiation steps as possible...

Estimation of α and short-term approximation

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Estimation of α and short-term approximation

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  - **Model II** u is $\pm$ constant:

$$s(t) = \frac{u_0}{\gamma} + \left(s_0 - \frac{u_0}{\gamma}\right) e^{-\gamma t}.$$

Long-term prediction

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Use of a Markov Model

Idea: flow of cells through manifold, following RNA velocities along close neighbours...

Research project

- Using RNA Velocity to detect genes significantly responsible for cellular differentiations

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- 2^{nd} application: study of a genetic disease ("S-cone enhanced Syndrome") and detection of genetic differences between healthy and ill patients

Thank you for your attention!

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