Some mathematical aspects of RNA velocity

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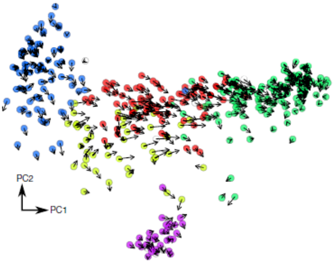
Purpose: summary of the mathematical aspects of the paper "*RNA velocity of single cells*" ([1])



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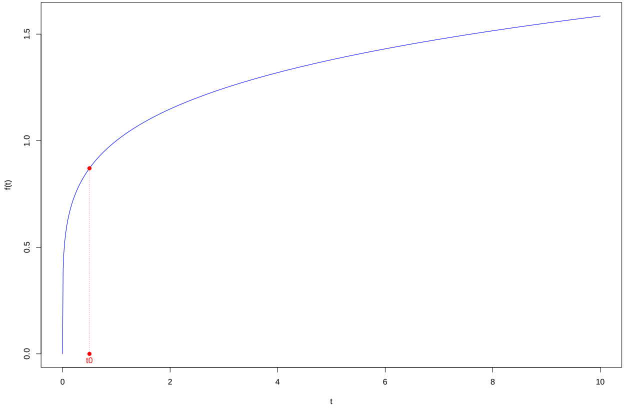

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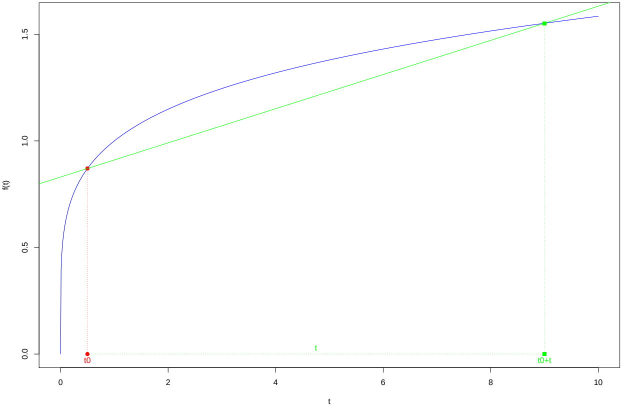

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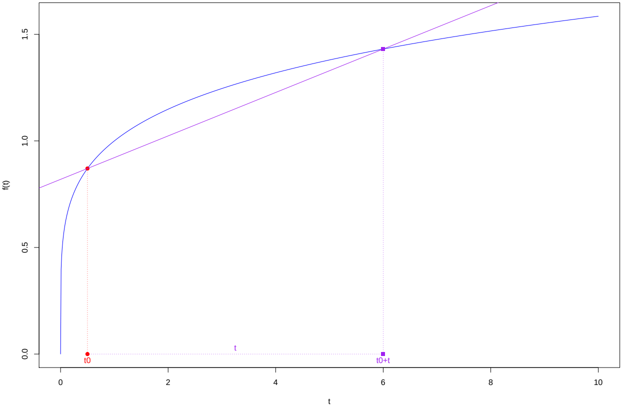

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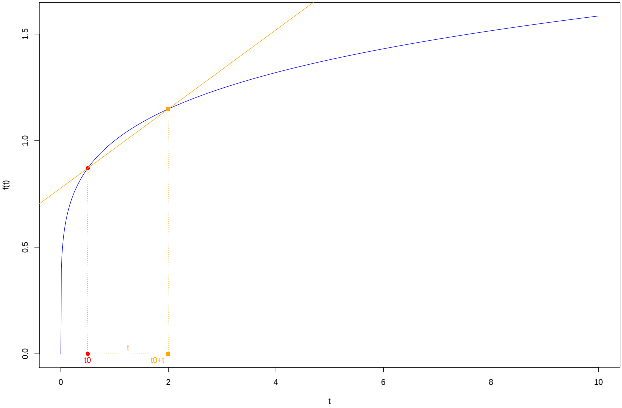

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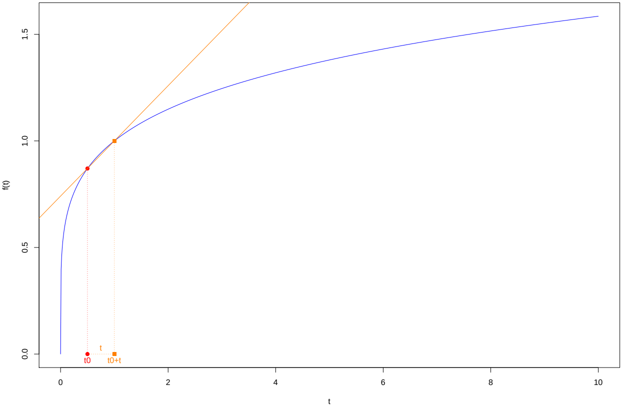

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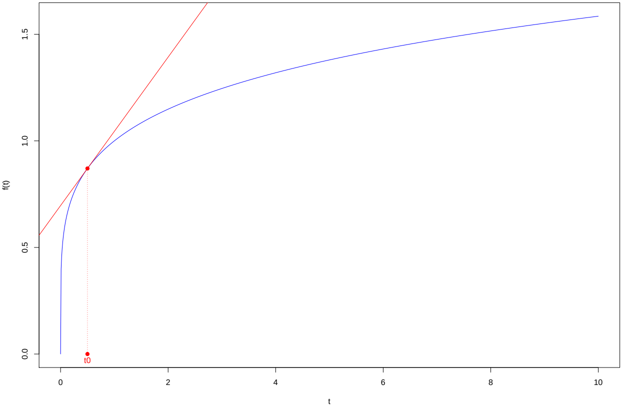

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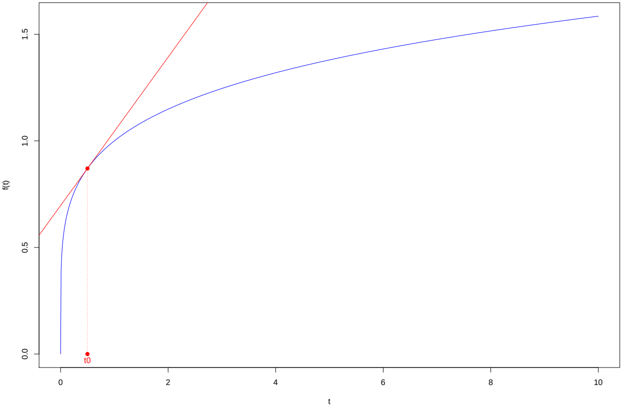

$$\frac{df}{dt}(t_0) := \lim_{t \to 0} \frac{f(t_0 + t) - f(t_0)}{t}$$

(if this limit exists and is finite).

Variations with respect to time

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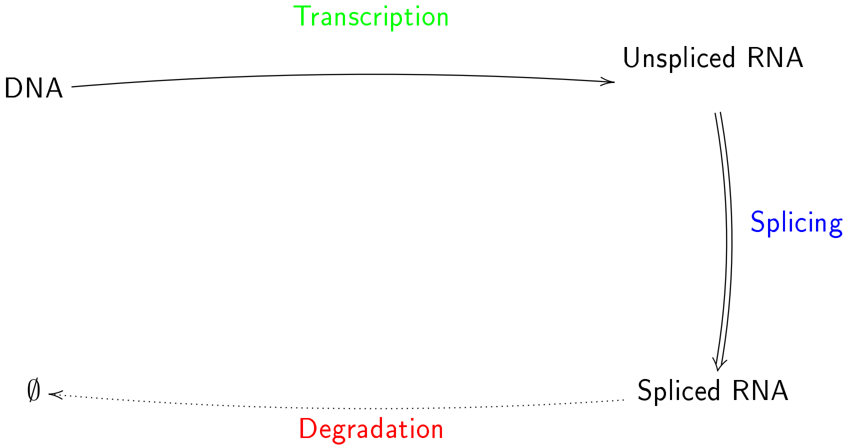
- In 3D: likewise! If $\vec{x}(t) := (x(t), y(t), z(t))$ is the position of a particle in the space, then its *velocity* is

$$\vec{v}(t) := \frac{d\vec{x}}{dt}(t) := \left(\frac{dx}{dt}(t), \frac{dy}{dt}(t), \frac{dz}{dt}(t)\right).$$

RNA dynamics: the idea

In <u>**one**</u> **cell**, for <u>**one**</u> **gene**...



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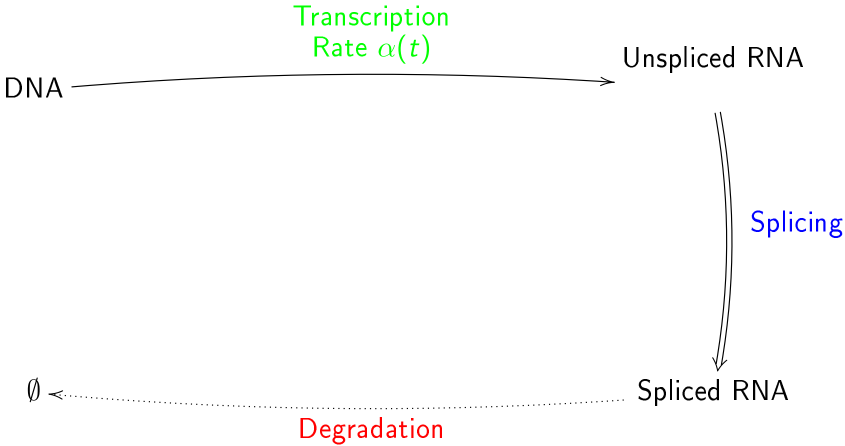

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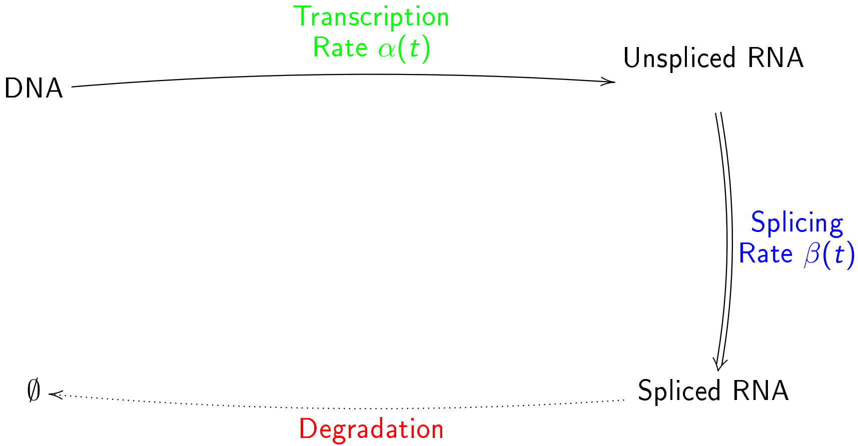

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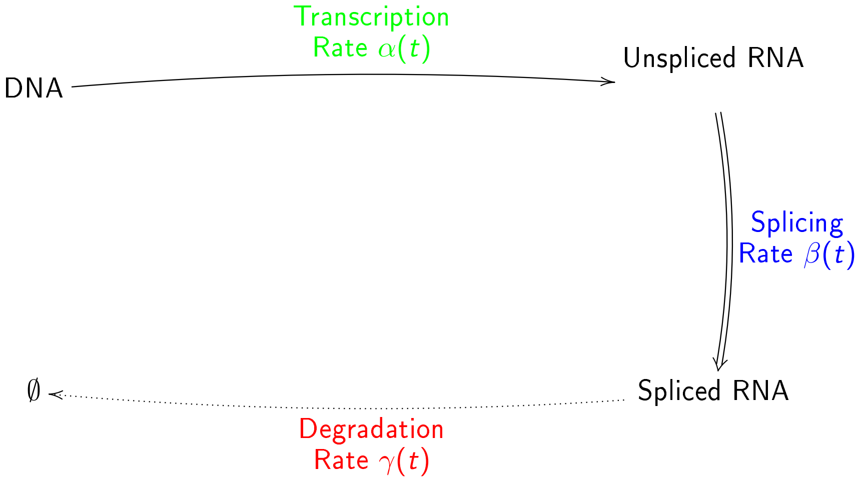

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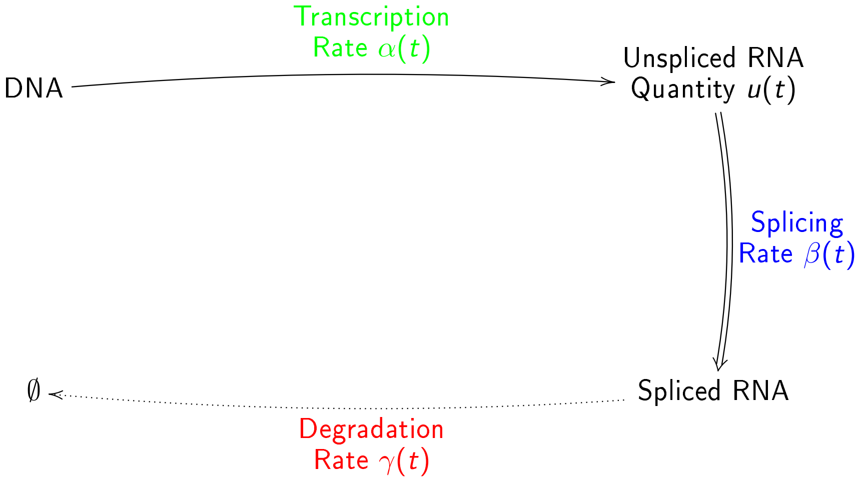

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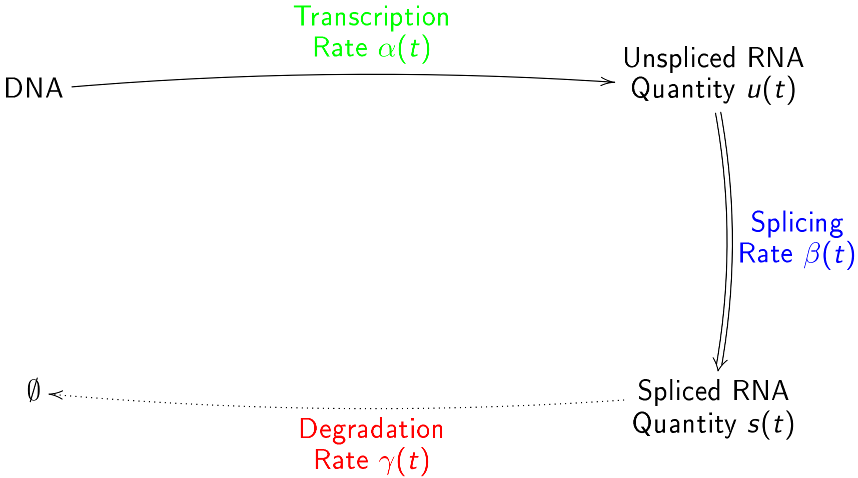

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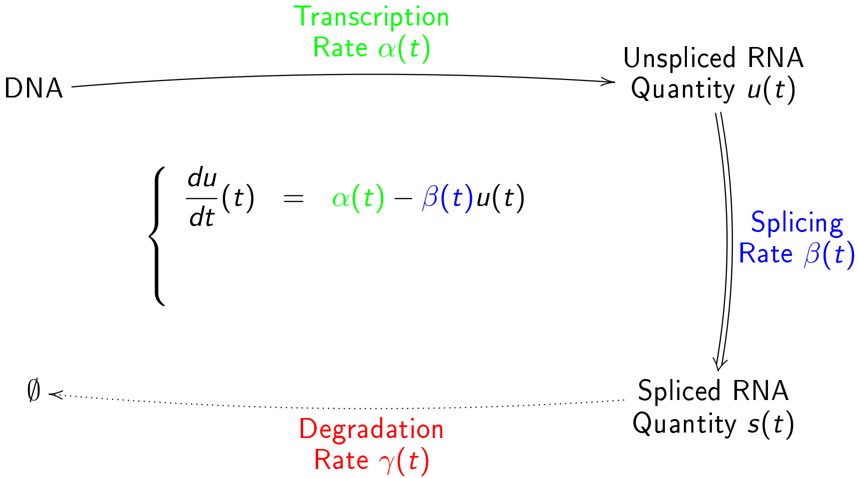

$$\begin{cases} \frac{du}{dt}(t) = \alpha(t) - \beta(t)u(t) \end{cases}$$

RNA dynamics: the idea

In **one cell**, for **one gene**...

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 $\beta(t)$

$\emptyset$ ← Spliced RNA
Quantity $s(t)$

Degradation
Rate $\gamma(t)$

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Our equations

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

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Assumptions

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Final equations

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"(Linear) differential equations"

Solution of the first equation

$$\frac{du}{dt}(t) = \alpha - u(t)$$

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If $u_0 := u(0)$,

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

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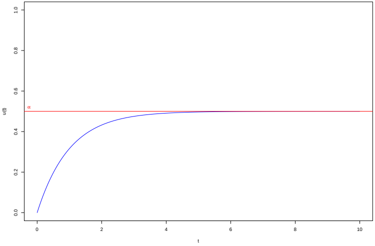

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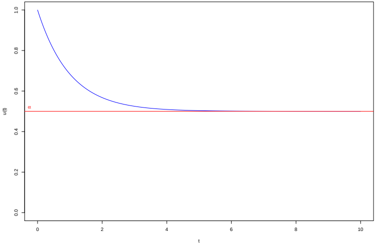

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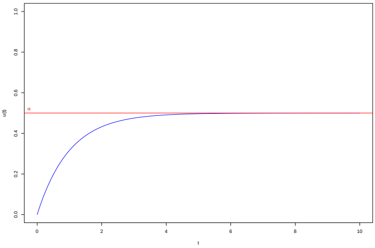

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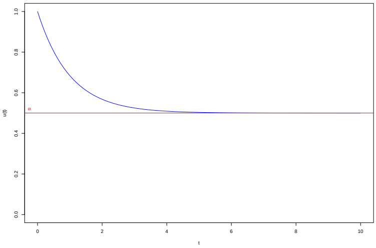

In all cases, $\lim_{t\to\infty} u(t) = \alpha$, i.e. $u(t) \approx \alpha$ if $t \gg 0$.

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

$$s(t) = \frac{\alpha}{\gamma} + \frac{u_0 - \alpha}{\gamma - 1} e^{-t} + \left(s_0 + \frac{\alpha - u_0}{\gamma - 1} - \frac{\alpha}{\gamma} \right) e^{-\gamma t}.$$

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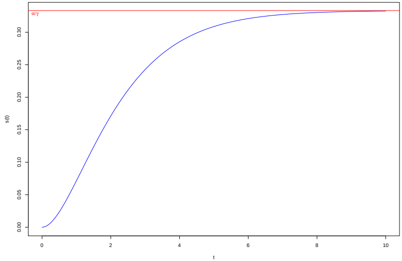
Many graphical possibilities... But we always have

$$\lim_{t \to \infty} s(t) = \frac{\alpha}{\gamma},$$

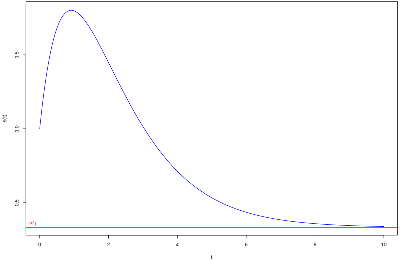
i.e. $s(t) \approx \frac{\alpha}{\gamma}$ if $t \gg 0$.

Solution of the second equation: graphical examples

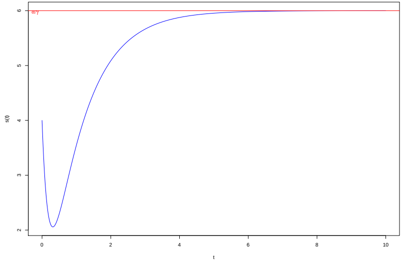
$u_0 = s_0 = 0, \ \alpha = 0.25, \ \gamma = 0.75$



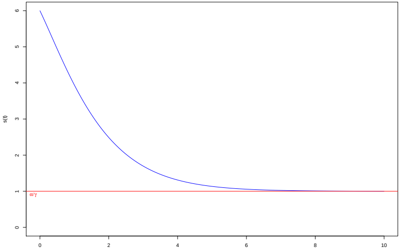
$u_0 = 3, \ s_0 = 1, \ \alpha = 0.25, \ \gamma = 0.75$



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



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



RNA dynamics: summary

There exist solutions u, s, depending on u_0, s_0 (initial conditions) and on α, γ (parameters), with

$$\lim_{t\to\infty} u(t) = \alpha \qquad \text{and} \qquad \lim_{t\to\infty} s(t) = \frac{\alpha}{\gamma}.$$

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Steady state

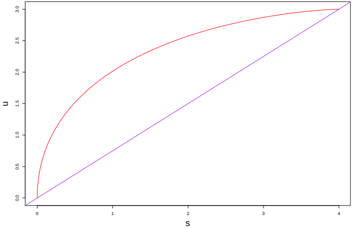
When $t \gg 0$, the system reaches a steady state, with

$$u(t) \approx \alpha, \qquad s(t) \approx \frac{\alpha}{\gamma}, \qquad \text{and} \qquad u(t) \approx \gamma s(t).$$

Phase portrait

Graphic "spliced vs. unspliced"

$u_0 = 0,\ s_0 = 0,\ \alpha = 3,\ \gamma = 0.75$



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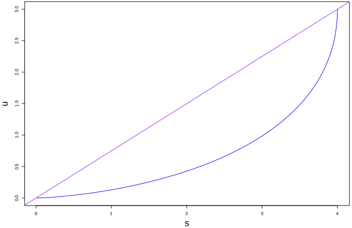

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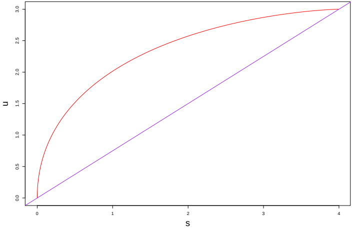

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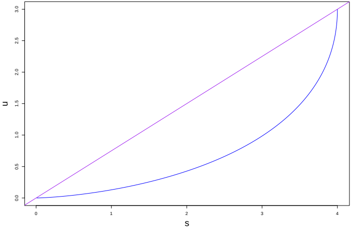

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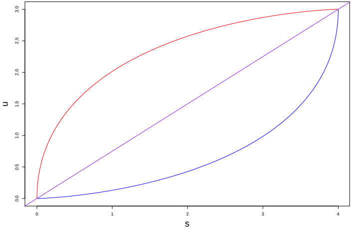

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Warning! Implicit assumption!

$\beta_j = 1$ for all j: the rates of splicing are equal for all genes!

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Definition

The *RNA velocity* of the cell (at time t) is

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

Representation: an unreal world...

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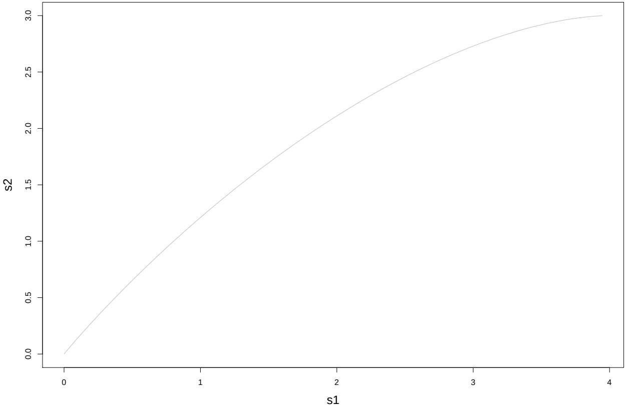

- Grey curve: trajectory of the cell $((s_1(t), s_2(t)))$.

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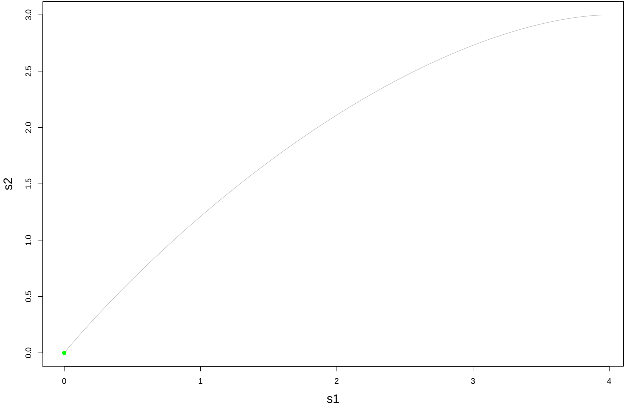

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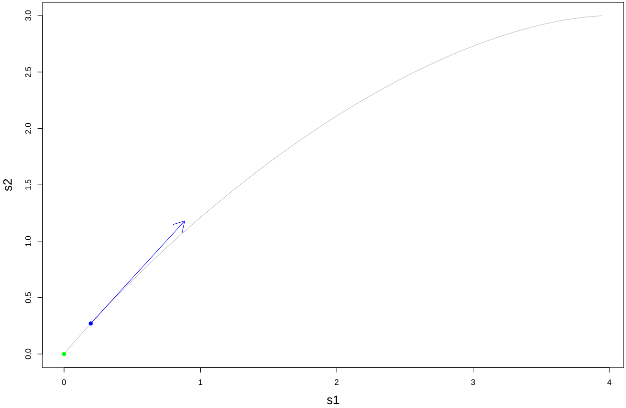

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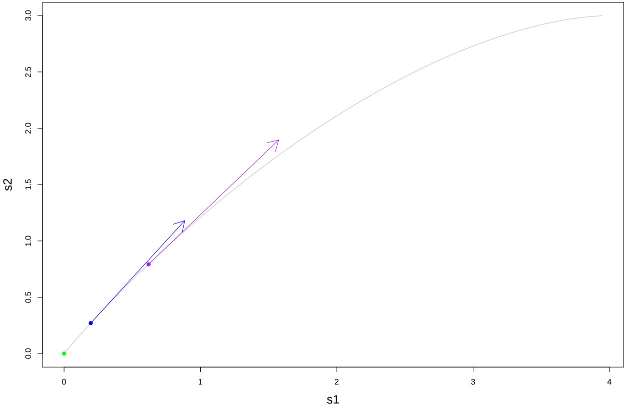

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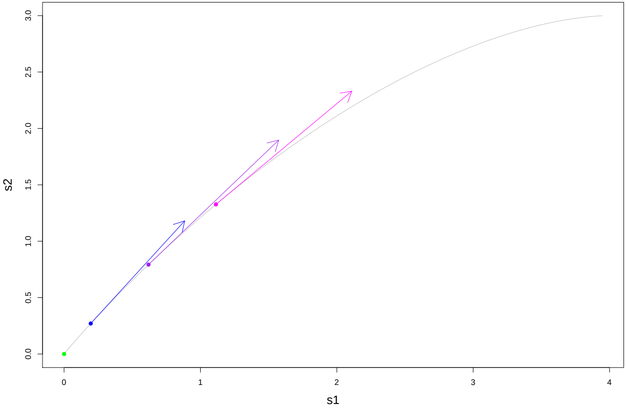

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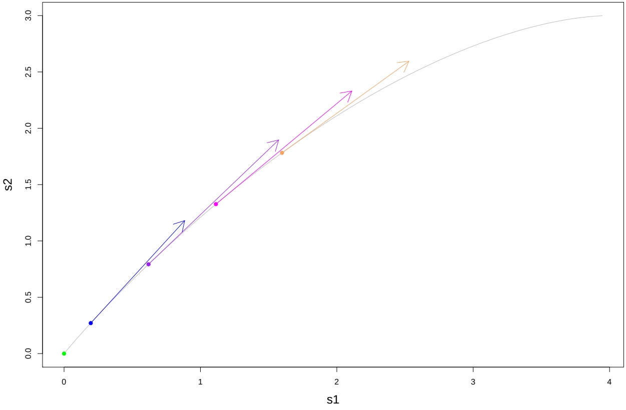

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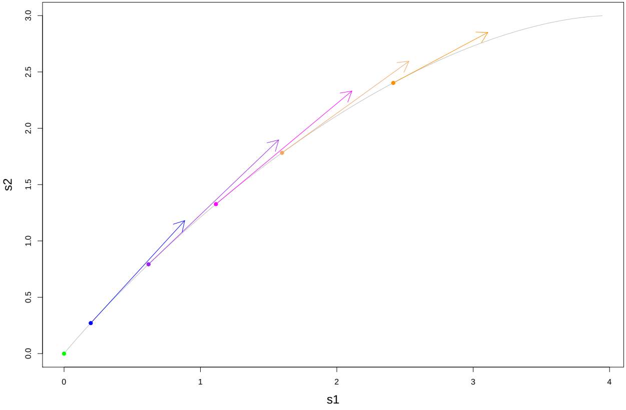

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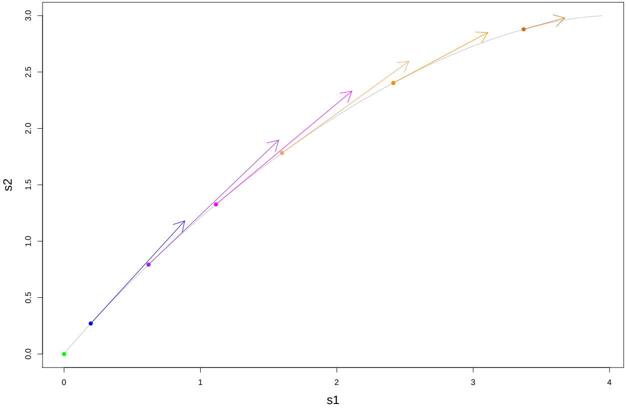

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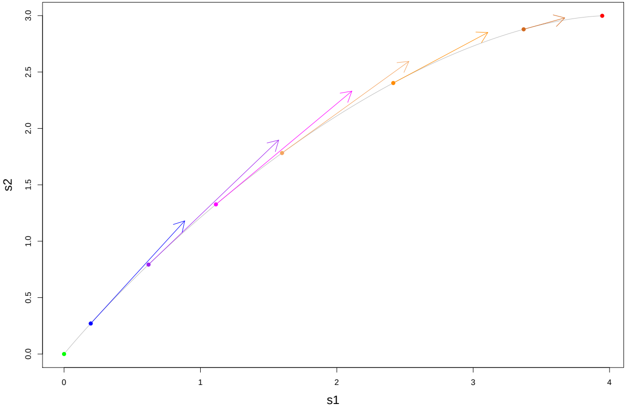

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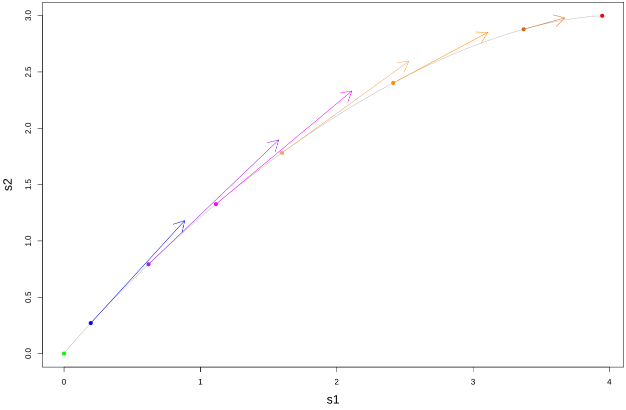

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"Physical velocity" in RNA's space!

Representation of RNA velocity

And if $p > 3$?

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- Principle component analysis: quite natural, projection on P.C.;

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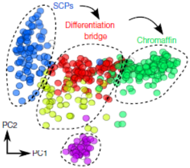
- t-SNE? Possible, but more tricky...

Representation of RNA velocity

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



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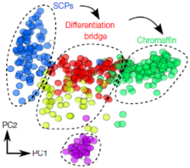

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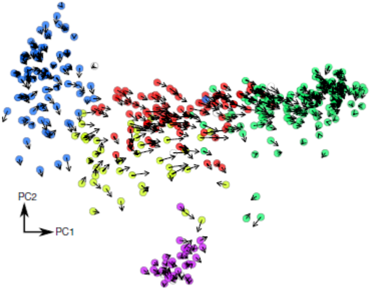

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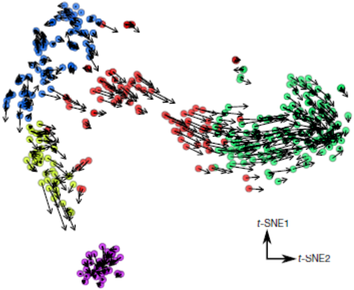

Estimation of γ

We study **one** gene (i.e. its parameters) through a sample of **several** cells.

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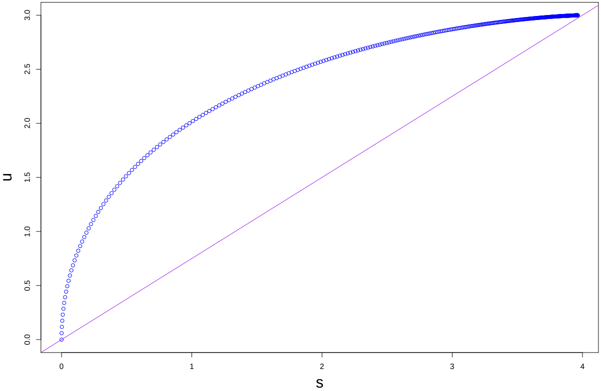
$\rightsquigarrow$ Estimation of γ with phase portraits...

Theoritical estimation of γ



- $\alpha = 3, \ \gamma = 0.75$
- Steady state: $u = \gamma s$
- 400 cells, uniformly generated in time.

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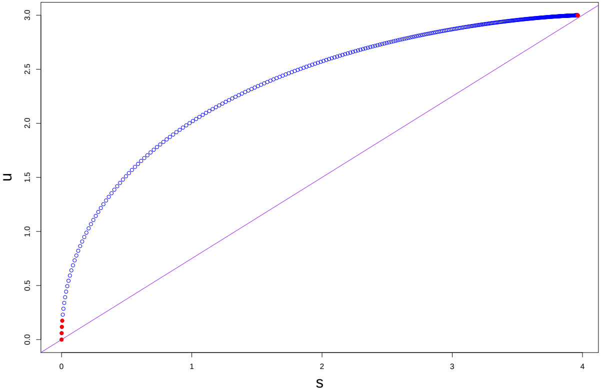

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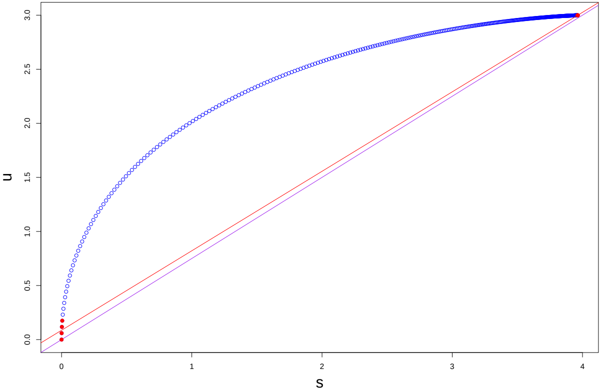

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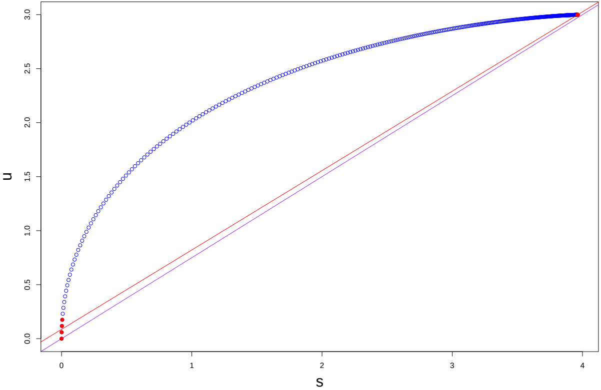

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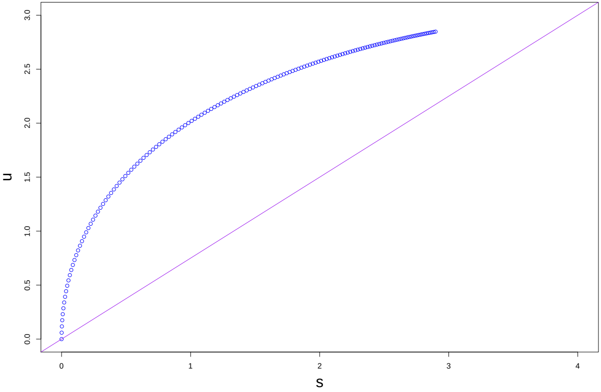
Here, estimation of γ (slope): 0.73493

Difficulties of estimation for γ...

Assumption 1 not respected...



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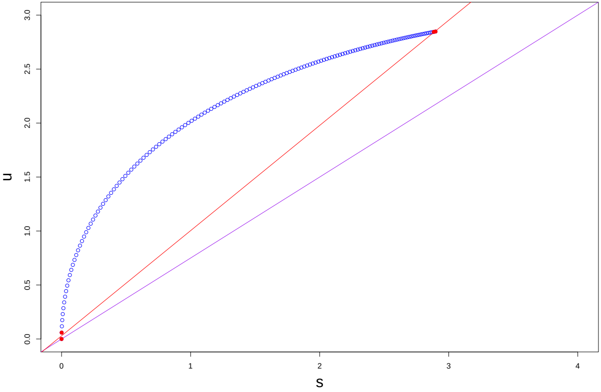

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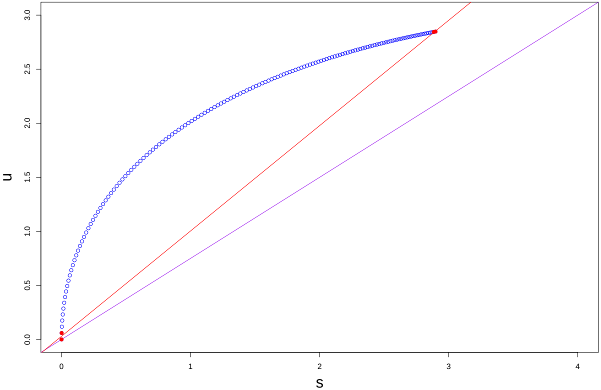

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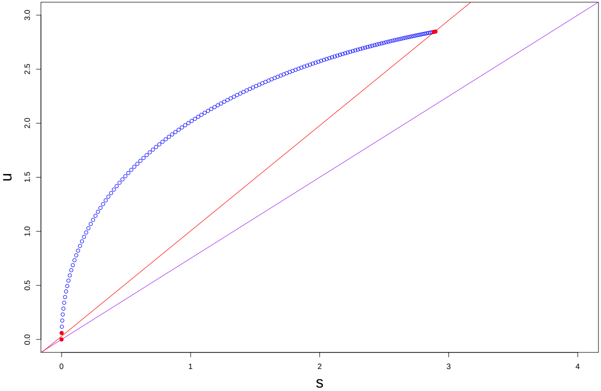

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Corrections?

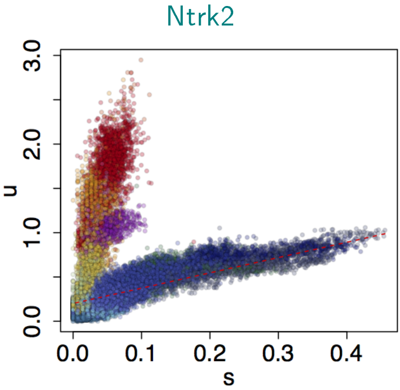
Estimation on very correlated genes, filtering some cells...

Multiple splicing

- In [1], $\pm$ 89 % of studied genes showed a unique degradation rate γ...

Multiple splicing

- In [1], $\pm$ 89 % of studied genes showed a unique degradation rate γ... but 11 % showed several degradation rates!
- Example from [1]:



- Then the model fails...

Estimation of α

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These two models are correct in the short term; they have to be used “step by step” to predict the future (Markov process).

Thank you for your attention!

Some recalls

A mathematical model

RNA velocity

Estimation of parameters and prediction

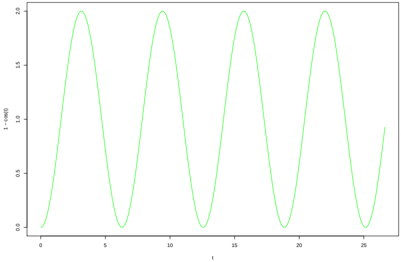
Appendix

And if the parameters are non-constant?

Much more complex...

Example

Assume that $\alpha(t) = 1 - \cos(t)$, $\beta = 1$, and $\gamma > 0$ is constant.



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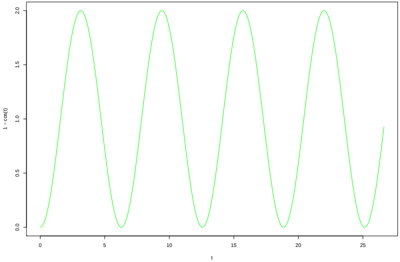


RNA equations

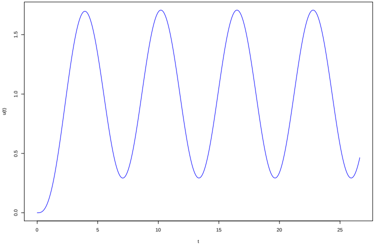
$$\begin{cases} \dfrac{du}{dt}(t) & = & [1 - \cos(t)] - u(t) \\ \dfrac{ds}{dt}(t) & = & u(t) - \gamma s(t) \end{cases}$$

Solutions

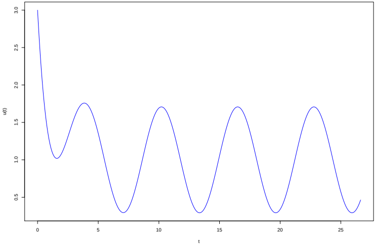
Unspliced RNA

$$u(t) = 1 - \frac{1}{2}(\cos(t) + \sin(t)) + \left(u_0 - \frac{1}{2}\right) e^{-t}.$$

$u_0 = 0$



$u_0 = 3$



Solutions

Spliced RNA

If $\gamma \neq 1$,

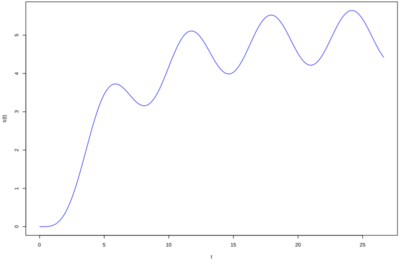
$$s(t) = \frac{1}{\gamma} - \frac{1}{2(1+\gamma^2)} \left((\gamma-1)\cos(t) + (\gamma+1)\sin(t)\right) + \frac{u_0 - 1/2}{\gamma - 1} e^{-t} + \left(s_0 - \frac{1}{\gamma} + \frac{1/2 - u_0}{\gamma - 1} + \frac{\gamma - 1}{2(1+\gamma^2)}\right) e^{-\gamma t}$$

and, if $\gamma = 1$,

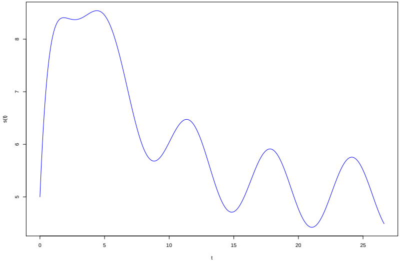
$$s(t) = 1 - \frac{1}{2}\sin(t) + \left(\left(u_0 - \frac{1}{2}\right) t + s0 - 1\right) e^{-t}.$$

Solutions

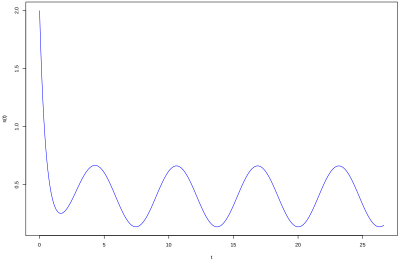
$u_0 = s_0 = 0, \quad \gamma = 0.2$



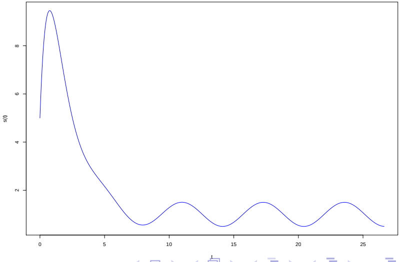
$u_0 = 7, \ s_0 = 5, \ \gamma = 0.2$



$u_0 = 1, \ s_0 = 2, \ \gamma = 2.5$

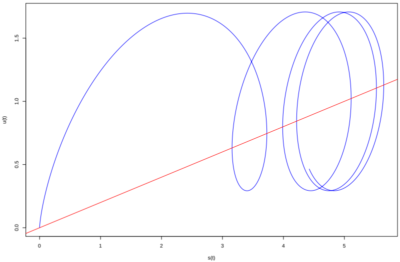


$u_0 = 20, \ s_0 = 5, \ \gamma = 1$



Phase portraits

$u_0 = s_0 = 0, \quad \gamma = 0.2$



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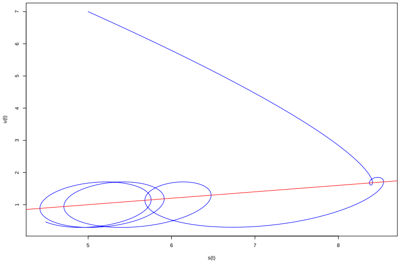
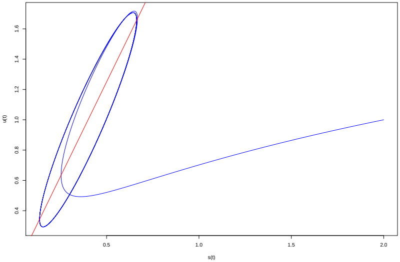


$u_0 = 1, \ s_0 = 2, \ \gamma = 2.5$



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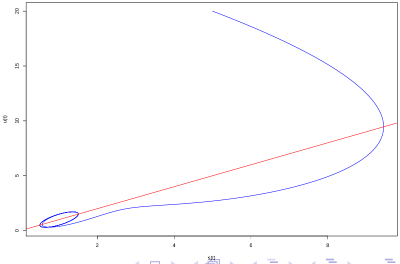

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Nature, 560:494–516, 2018.