

# Differential Equations and Transcriptional Dynamics of RNA

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收录于话题

#ODE 1 #RNA速率 1

## Part 1: Basic Introduction about RNA Velocity

The research [paper<sup>\[1\]</sup>](#) proposes a model which describes a certain transcriptional dynamics pattern of mRNA.

Given one specific gene in one cell, we have unspliced, say, precursor mRNAs with quantity  $u(t)$ , which will be spliced into mature mRNAs with quantity  $s(t)$  at the rate  $\beta$ , as the research paper describes, removing introns from pre-mRNAs and joining adjacent exons to produce spliced mRNAs. Eventually, these spliced mRNAs will be degraded with the rate  $\gamma(t)$ .

Let's now assume the rates of splicing and degradation are constant and time-independent. We get the following linear differential equations:

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

$$\frac{ds(t)}{dt} = \beta u(t) - \gamma s(t)$$

which describes how the mRNA abundances evolve over time. In this context,  $u(t)$  and  $s(t)$  are the expected values of the quantities of molecules of unspliced and spliced mRNA at the specific time point  $t$ .

## Part 2: Solve the Differential Equations Above

### For Equation 1

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

$$-\frac{1}{\beta} \ln |\alpha - \beta u(t)| + c_1 = t + c_2$$

$$-\frac{1}{\beta} \ln |\alpha - \beta u(t)| = t + c_2 - c_1$$

$$\ln |\alpha - \beta u(t)| = -\beta t + [-\beta \times (c_2 - c_1)]$$

**Assume**  $\ln c_3 = -\beta \cdot (c_2 - c_1)$

$$e^{\ln |\alpha - \beta u(t)|} = e^{-\beta t + \ln c_3}$$

If  $\alpha > \beta u(t)$ ,  $\alpha - \beta u(t) = c_3 e^{-\beta \cdot t}$

$$u(t) = \frac{\alpha - c_3 e^{-\beta \cdot t}}{\beta}$$

Given  $t = 0$ , We get  $u(0) = \frac{\alpha - c_3}{\beta}$

$$c_3 = \alpha - \beta u(0)$$

Let's substitute  $c_3$  back to  $u_t$

$$u(t) = \frac{\alpha - [\alpha - \beta u(0)] \cdot e^{-\beta t}}{\beta} = u(0) \cdot e^{-\beta t} + \frac{\alpha}{\beta} (1 - e^{-\beta t})$$

**For Equation 2**

$$\frac{ds(t)}{dt} + \gamma s(t) = \beta u(t)$$

According to the book [Differential Equations with Applications and Historical Notes<sup>\[2\]</sup>](#) written by G.F.Simmons. We should consider applying the substitution  $y = uv$  to the homogeneous equation  $y'' + P(x)y' + Q(x)y = 0$ .

$$s(t) = uv \frac{ds(t)}{dt} = u \frac{dv}{dt} + v \frac{du}{dt}$$

$$u \frac{dv}{dt} + v \frac{du}{dt} + \gamma uv = \beta u(t)$$

$$u \frac{dv}{dt} + v \left( \frac{du}{dt} + \gamma u \right) = \beta u(t)$$

Assume  $\frac{du}{dt} + \gamma \cdot u = 0$

$$\frac{du}{dt} = -\gamma \cdot u$$

$$\ln u = -\gamma \cdot t + C$$

$$\int \frac{du}{dt} = - \int \gamma dt$$

Assume  $C = -\ln k$

$$\ln u + \ln k = -\gamma \cdot t$$

$$u \cdot k = e^{-\gamma \cdot t}$$

$$u = \frac{e^{-\gamma \cdot t}}{k}$$

Then we substitute u back to the equation above.

$$\frac{e^{-\gamma \cdot t}}{k} \cdot \frac{dv}{dt} = \beta u(t)$$

$$dv = \frac{\beta \cdot k \cdot u(t)}{e^{-\gamma t}} dt$$

$$dv = \frac{\beta \cdot k \cdot \left[ u(0) \cdot e^{-\beta t} + \frac{\alpha}{\beta} (1 - e^{-\beta t}) \right]}{e^{-\gamma t}} dt$$

$$dv = \frac{[k \cdot \beta \cdot u(0)] \cdot e^{-\beta t} + \alpha \cdot k \cdot (1 - e^{-\beta t})}{e^{-\gamma t}} dt$$

$$dv = \frac{(k \cdot \beta \cdot u(0)) \cdot e^{-\beta t} + \alpha k - \alpha k e^{-\beta t}}{e^{-\gamma \cdot t}} dt$$

$$dv = \frac{\alpha k + k[\beta u(0) - \alpha]e^{-\beta t}}{e^{-\gamma \cdot t}} dt$$

$$\int dv = k \int e^{\gamma t - \beta t} \cdot [\beta u(0) - \alpha] + \alpha \cdot e^{\gamma t} dt$$

$$v = \int e^{(\gamma - \beta)t} \cdot [\beta u(0) - \alpha] \cdot k dt + \int \alpha \cdot k \cdot e^{\gamma t} dt$$

$$v = k[\beta u(0) - \alpha] \int e^{(\gamma - \beta)t} dt + \alpha \cdot k \int e^{\gamma t} dt + k \cdot C$$

(Please note:  $kC$  is a constant, we choose it instead of  $C$  because we want the deduction more smoothly)

Continue:

$$v = k \left[ (\beta u(0) - \alpha) \frac{e^{(\gamma - \beta)t}}{\gamma - \beta} + \alpha \cdot \frac{e^{\gamma t}}{\gamma} + C \right]$$

$$s(t) = uv = \frac{e^{-\gamma t}}{k} k \left[ (\beta u(0) - \alpha) \cdot \frac{e^{(\gamma - \beta)t}}{\gamma - \beta} + \frac{\alpha \cdot e^{\gamma t}}{\gamma} + C \right]$$

$$s(t) = \frac{e^{-\beta t} \cdot [\beta u(0) - \alpha]}{\gamma - \beta} + \frac{\alpha}{\gamma} + C \cdot e^{-\gamma t}$$

$$C = s(0) - \frac{\beta u(0) - \alpha}{\gamma - \beta} - \frac{\alpha}{\gamma}$$

$$s(0) = \frac{\beta u(0) - \alpha}{\gamma - \beta} + \frac{\alpha}{\gamma} + C$$

Substitute  $s(0)$  back to  $s(t)$ , we get

$$s(t) = \frac{e^{-\beta t}(\beta u(0) - \alpha)}{\gamma - \beta} + \frac{\alpha}{\gamma} + \left[ s(0) - \frac{\beta u(0) - \alpha}{\gamma - \beta} - \frac{\alpha}{\gamma} \right] \cdot e^{-\gamma t}$$

$$s(t) = \frac{e^{-\beta t} \cdot [\beta u(0) - \alpha]}{\gamma - \beta} + \frac{\alpha}{\gamma} + s(0)e^{-\gamma t} - \frac{[\beta u(0) - \alpha] \cdot e^{-\gamma t}}{\gamma - \beta} - \frac{\alpha}{\gamma} e^{-\gamma t}$$

Finally,

$$s(t) = s(0)e^{-\gamma t} + \frac{\alpha}{\gamma} (1 - e^{-\gamma t}) + \frac{\beta u(0) - \alpha}{\gamma - \beta} (e^{-\beta t} - e^{-\gamma t})$$

Replace  $t$  with  $\tau$  and given  $\tau = t - t_0^{(k)}$

$k$  is the transcriptional state of the cell.

**Dynamical model. Model description.** In recognition that steady states are not always captured and that splicing rates differ between genes, we establish a framework that does not rely on these restrictions. The analytical solution to the gene-specific rate equations in Equation 1 is found by integration, which yields

$$\begin{aligned} u(t) &= u_0 e^{-\beta\tau} + \frac{\alpha^{(k)}}{\beta} (1 - e^{-\beta\tau}), \\ s(t) &= s_0 e^{-\gamma\tau} + \frac{\alpha^{(k)}}{\gamma} (1 - e^{-\gamma\tau}) + \frac{\alpha^{(k)} - \beta u_0}{\gamma - \beta} (e^{-\gamma\tau} - e^{-\beta\tau}), \tau = t - t_0^{(k)}, \end{aligned} \quad (4)$$

with parameters of reaction rates  $\theta = (\alpha^{(k)}, \beta, \gamma)$ , cell-specific time points  $t \in (t_1, \dots, t_N)$  and initial conditions  $u_0 = u(t_0)$ ,  $s_0 = s(t_0)$ .

Gene activity is orchestrated by transcriptional regulation, implying that gene upregulation and downregulation are inscribed by alterations in the state-dependent transcription rate  $\alpha^{(k)}$ . That is,  $\alpha^{(k)}$  can have multiple configurations each encoding one transcriptional state. For the model, this requires an additional parameter set, assigning a transcriptional state  $k$  to each cell. Consequently, not only  $\alpha^{(k)}$  but also the initial conditions  $u_0^{(k)}$ ,  $s_0^{(k)}$  are state dependent, as well as the time point of switching states  $t_0^{(k)}$ . In the following, we consider four phases, induction ( $k = 1$ ) and repression ( $k = 0$ ), each with an associated potential steady state ( $k = ss_1$  and  $k = ss_0$ ). Consider a transition from one state  $k$  to a subsequent state  $k'$ —for example, from induction to repression. Then, the initial conditions of the next state are given by evaluating the trajectory of the current state at its respective switching time point

$$\begin{aligned} u_0^{(k')} &= u(t_0^{(k')} | \theta^{(k)}), \\ s_0^{(k')} &= s(t_0^{(k')} | \theta^{(k)}), \end{aligned} \quad (5)$$

where  $t_0^{(k')}$  is learned jointly with the parameters of reaction rates, as will be described later.

Being at state  $k$ , abundances can potentially reach their steady state in the limit

$$(u_\infty^{(k)}, s_\infty^{(k)}) = \left( \frac{\alpha^{(k)}}{\beta}, \frac{\alpha^{(k)}}{\gamma} \right). \quad \text{CompBioLab} \quad (6)$$

Wait a minute, remember we only assume  $\alpha > \beta u(t)$ , thus  $\alpha - \beta u(t) = c_3 e^{-\beta \cdot t}$ , I guess we should also consider  $\alpha < \beta u(t)$  as well, isn't it?

## Acknowledgment

*Some mathematical aspects of RNA velocity* by Loïc DEMEULENAERE at Université de Liège

The cover came from the documentation of scVelo (<https://scvelo.readthedocs.io/>).

## References

- [1] paper: <https://doi.org/10.1038/s41587-020-0591-3>
- [2] Differential Equations with Applications and Historical Notes: <https://doi.org/10.1201/9781315371825>