Network RNA Velocity

Boya Hou

University of Illinois Urbana-Champaign

Joint work with Prof. Maxim Raginsky, Dr. Abhishek Pandey, Prof. Olgica Milenkovic

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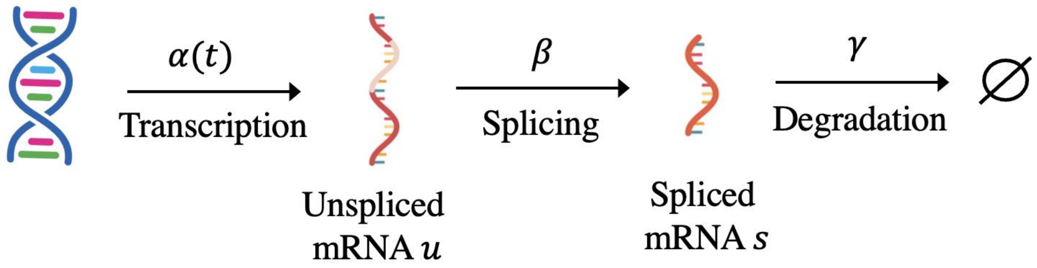
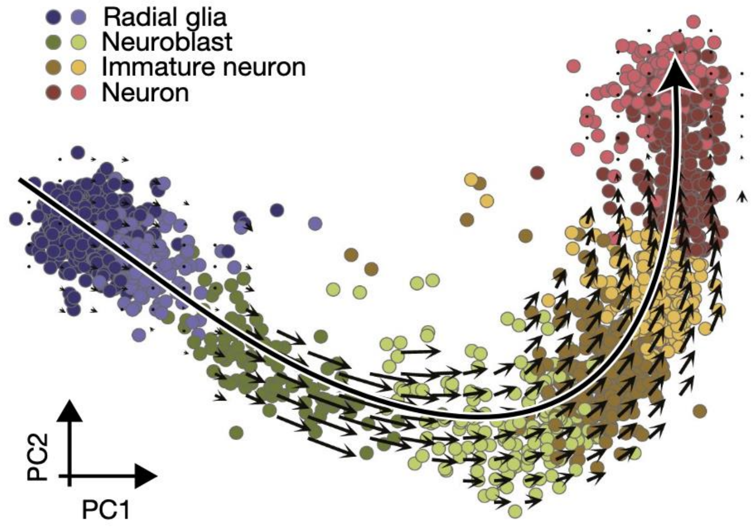
DNA Transcription



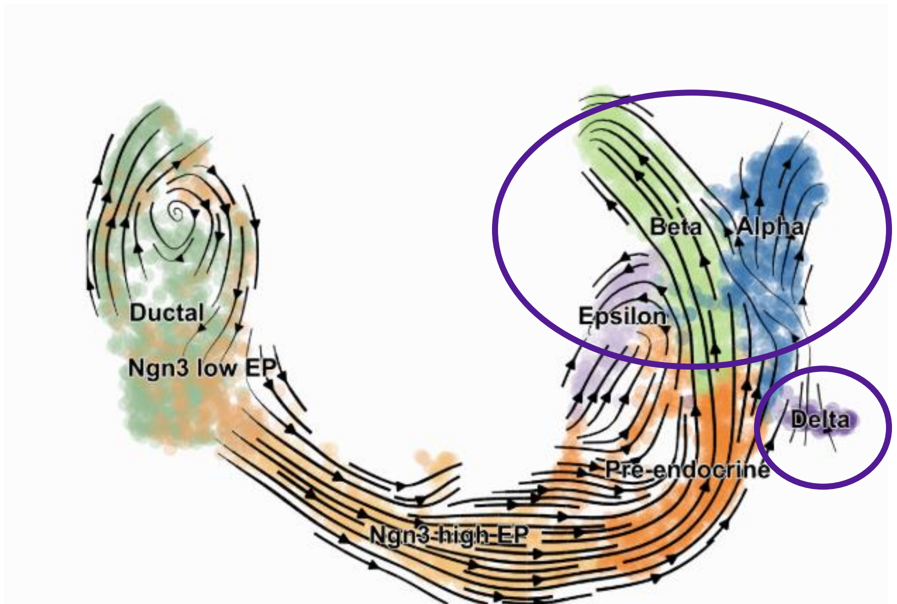
Unspliced $$\frac{du}{dt} = \alpha(t) - \beta u(t)$$

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

RNA velocity (La Manno et al., 2018) $$v(t) = \frac{ds}{dt} = \beta u(t) - \gamma s(t)$$



La Manno et al. 2018



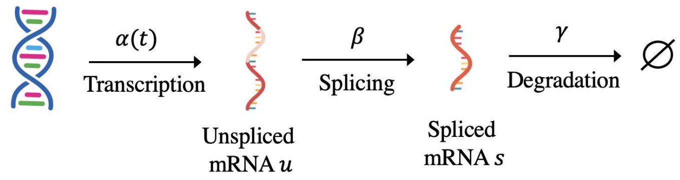
Bergen et al. 2020

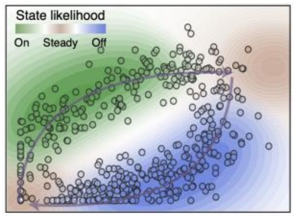
La Manno et al. "RNA velocity of single cells." *Nature* 560.7719 (2018): 494-498.

Bergen, Volker, et al. "Generalizing RNA velocity to transient cell states through dynamical modeling." Nature biotechnology 38.12 (2020): 1408-1414.

Gorin, G., Fang, M., Chari, T., & Pachter, L. (2022). RNA velocity unraveled. *PLOS Computational Biology*, *18*(9), e1010492.

Models of RNA Velocity



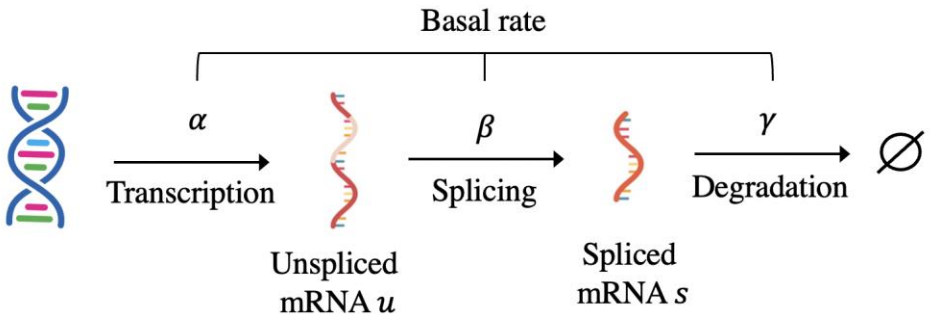
Model	Model Description	Limitation
Velocyto [Manno et al. 2018]	Steady-state ratio of unspliced to spliced RNA: $\frac{\gamma}{\beta}$. Velocity: $v = u - \frac{\gamma}{\beta}$ s.	Assumes a steady-state model.
scVelo [Bergen et al. 2020] 	Full dynamical model: $u(t) = u_0 e^{-\beta\tau} + \frac{\alpha^{(k)}}{\beta}\left(1 - e^{-\beta\tau}\right), \quad \tau = t - t_0^{(k)}$ $s(t) = s_0 e^{-\gamma\tau} + \frac{\alpha^{(k)}}{\gamma}\left(1 - e^{-\gamma\tau}\right) + \frac{\alpha^{(k)} - \beta u_0}{\gamma - \beta}\left(e^{-\gamma\tau} - e^{-\beta\tau}\right).$	Treats each gene independently and regulatory relationships are ignored.
TFVelo [Li et al. 2024]	Transcription factor-aware: $y_g(t) = \alpha_g \sin(\omega_g t + \theta_g) + \beta_g,$ $\frac{dy_g(t)}{dt} = W_g X_g(t) - \gamma_g y_g(t).$	• Assume a specific behavioral form (sine function). • Does not explicitly integrate GRNs as transcription rate controllers.

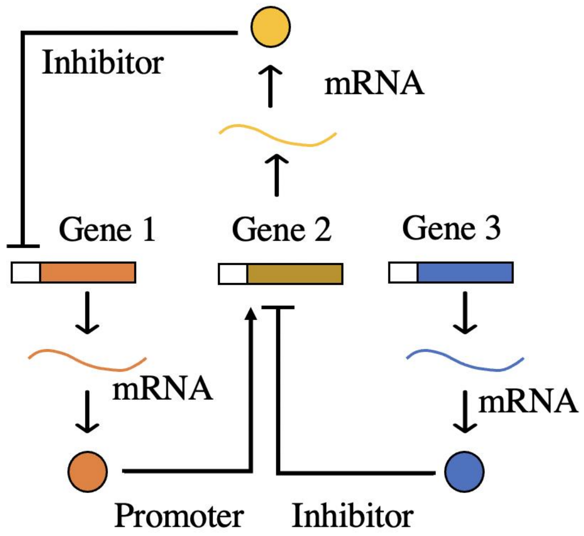
La Manno et al. "RNA velocity of single cells." *Nature* 560.7719 (2018): 494-498.

Bergen, Volker, et al. "Generalizing RNA velocity to transient cell states through dynamical modeling." Nature biotechnology 38.12 (2020): 1408-1414.

Li, Jiachen, et al. "TFvelo: gene regulation inspired RNA velocity estimation." Nature Communications 15.1 (2024): 1387.

Our Model for Network RNA Velocity





Gene Regulatory Network

Unspliced $$\frac{du_i^g}{dt} = \alpha_i^g \frac{\kappa + \sum_{q=1}^{n_g} W_{gq}^{+} s_i^q(t)}{\kappa + \sum_{q=1}^{n_g} W_{gq}^{-} s_i^q(t)} - \beta_i^g u_i^g(t),$$

Spliced $$\frac{ds_i^g}{dt} = \beta_i^g u_i^g(t) - \gamma_i^g s_i^g(t) + \frac{c}{n_c} \sum_{j=1}^{n_c} a_{ij} \left(s_j^g(t) - s_i^g(t) \right)$$

Intercellular Network (not in this talk)

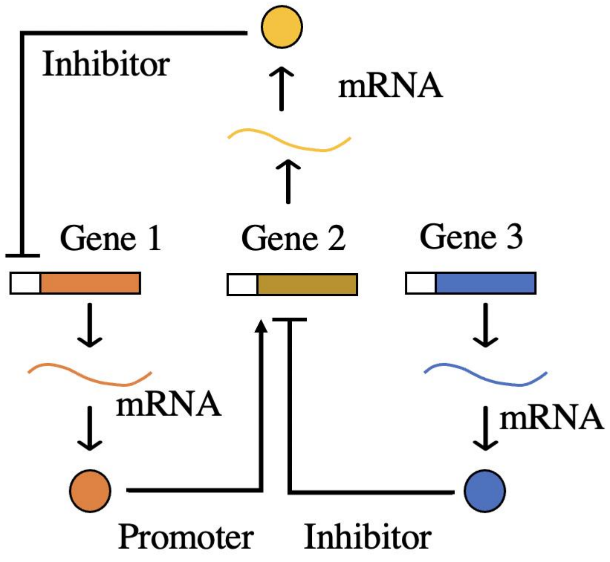
Goal: Study network RNA velocity and targeted drug interventions (in collaboration with AbbVie).

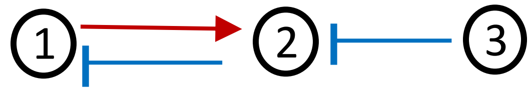
Incremental Gain and the Sign of Regulation in GRNs

Unspliced $\frac{du^g}{dt} = \alpha^g \frac{\kappa + \sum_{q=1}^{n_g} W_{gq}^{+} s^q(t)}{\kappa + \sum_{q=1}^{n_g} W_{gq}^{-} s^q(t)} - \beta^g u^g(t),$

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

$$R_g(s) := \frac{\kappa + \sum_{q=1}^{n_g} W_{gq}^{+} s^q(t)}{\kappa + \sum_{q=1}^{n_g} W_{gq}^{-} s^q(t)} = \frac{N_g(s)}{D_g(s)}$$





A graph model of GRN

The incremental gain of R_g due to a change from s^q to $\hat{s}^q$ is

$$\frac{R_g(s) - R_g(\hat{s})}{s^q - \hat{s}^q} = \frac{D W_{gq}^{+} - N W_{gq}^{-}}{D D'}$$

The incremental gain will be:

positive if $W_{gq}^{+} > 0$ (and thus $W_{gq}^{-} = 0$), and negative if $W_{gq}^{-} > 0$ (and thus $W_{gq}^{+} = 0$) .

Existence of Steady States

Unspliced
$$\frac{du^g}{dt} = \alpha^g \frac{\kappa + \sum_{q=1}^{n_g} W_{gq}^{+} s^q(t)}{\kappa + \sum_{q=1}^{n_g} W_{gq}^{-} s^q(t)} - \beta^g u^g(t),$$

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

For a nonlinear system $\frac{dx}{dt} = f(x)$, a point x_e is a steady state if $f(x_e) = 0$.

System is globally asymptotically stable if for every trajectory $x(t)$, we have $x(t) \rightarrow x_e$ as $t \rightarrow \infty$.

Theorem 1:

Suppose that $\beta_g > 0$ and $\gamma_g > 0$ for all genes g. Let $C = \max_g \sum_{q=1}^{n_g} W_{gq}^{+}$ and $\xi = \max_g \frac{\alpha^g}{\gamma^g}$.

The networked dynamics admits a steady state (u^*, s^*) if $\kappa \geq C\xi$.

Stability — Single Gene Case

What does it mean for a system to be stable?

Suppose a system has a steady state (u^*, s^*). If you slightly perturb the system, does it:

Return to the steady state (Stable) ? Or drift away over time (Unstable)?

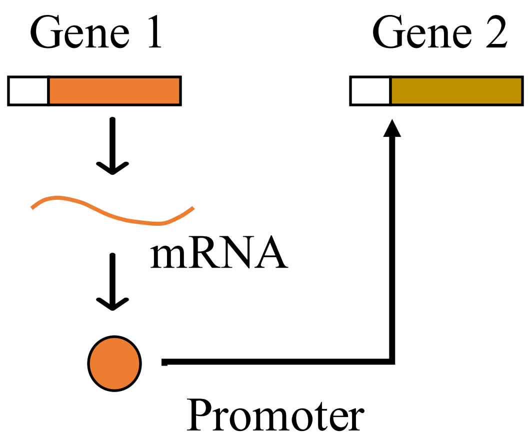
Example of a system with stable steady states: bacteriophage lambda lysogenic maintenance circuits, drosophila segment polarity network, etc.

$$\frac{d}{dt}\begin{bmatrix} u \\ s \end{bmatrix} = \underbrace{\begin{bmatrix} -\beta & 0 \\ \beta & -\gamma \end{bmatrix}}_{=A} \begin{bmatrix} u \\ s \end{bmatrix} + \begin{bmatrix} \alpha \\ 0 \end{bmatrix}.$$

Linear system, globally asymptotic stable iff $\mathcal{R}e(\lambda(A)) < 0$.

Eigenvalues of A: $\lambda_1 = -\beta < 0$, $\lambda_2 = -\gamma < 0$. Thus, the system is always stable.

Stability of Promoter-Only GRNs



A pure positive regulation network

$$\frac{du^g}{dt} = \alpha^g \left(\kappa + \sum_{q=1}^{n_g} W_{gq}^{+} s^q(t) \right) - \beta^g u^g(t)$$

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

Linear system, we can write it as $\dot{x} = Ax$, $x = \binom{u^g}{s^g}$.

The linear system $\dot{x} = Ax$ is globally asymptotic stable iff $\mathcal{Re}(\lambda(A)) < 0$.

Lemma 1: Suppose the condition of Theorem 1 holds s.t. a steady state exists.

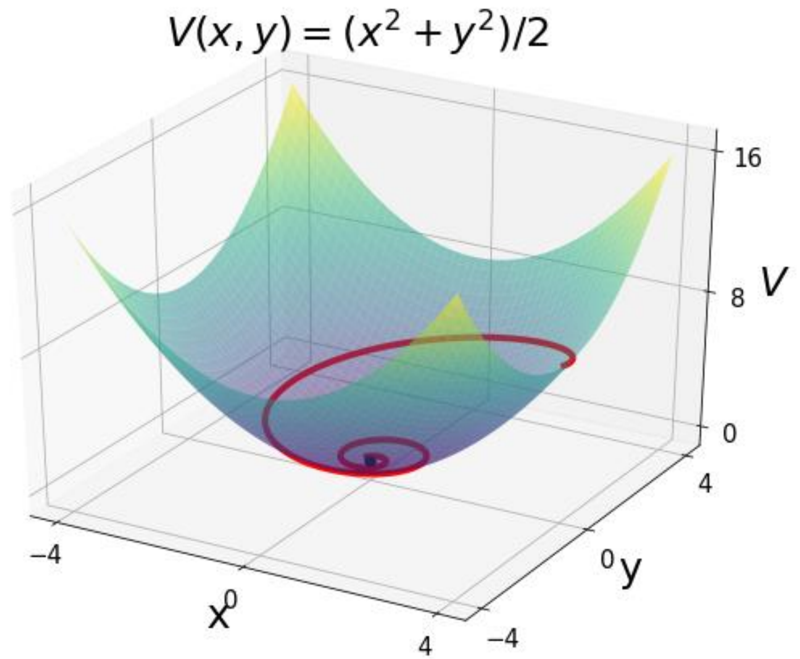
When there is no inhibitor, i.e., $W_{gq}^{-} = 0$ for all genes, the networked dynamics is stable

if, $\gamma_g > \beta_g > \alpha_g \sum_{h=1}^{n_g} W_{gh}^{+}$, for all g.

General Case: Understanding Stability via Lyapunov Functions

Goal: make conclusions about trajectories of a system $\dot{x} = f(x)$ (e.g., globally asymptotically stable). without finding the trajectories (i.e., solving the differential equations).

Consider a nonlinear system $\dot{x} = f(x)$.



A Lyapunov global asymptotic stability theorem:

Suppose there exists a function $V: R^n \rightarrow R$ that is positive definite, i.e., $V(x) \geq 0$ for all x, $V(x) = 0$ iff $x = x_e$,

and $V(x) \rightarrow \infty$ whenever $||x|| \rightarrow \infty$.

In addition, $\dot{V}(x) < 0$ for all $x \neq x_e$, and $\dot{V}(x_e) = 0$.

Then, every trajectory of $\dot{x} = f(x)$ converges to x_e as $t \rightarrow \infty$.

We call V a Lyapunov function, which can be thought of as a generalized energy function.

Stability of Network RNA Velocity

Theorem 2: Suppose the condition of Theorem 1 holds s.t. a steady state exists.

Consider a positive semi-definite function as a candidate Lyapunov function,

$$V(u,s) := \frac{1}{2}\|u-u^*\|_2^2 + \frac{1}{2}\|s-s^*\|_2^2$$

Suppose there is sufficient negative regulation in the network, i.e., there exists $\delta > 0$ s.t.

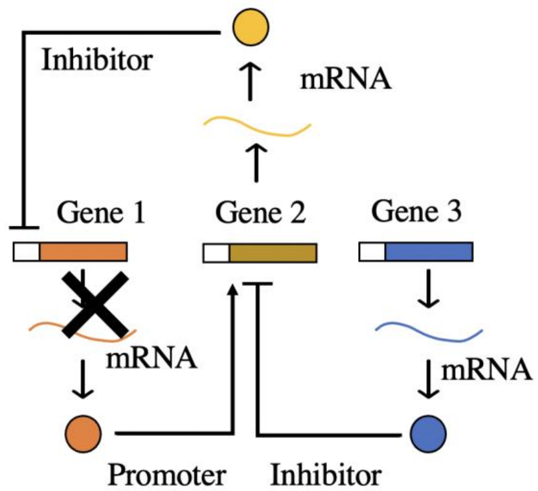
$$\min_g \sum_{q=1}^{n_g} W_{gq}^{-} s^q \geq \delta \left(\sum_{q=1}^{n_g} s^q \right).$$

If for some constant ω that depends on the GNR, the parameters satisfy

$$\beta^g > \frac{\omega\|\alpha\|}{2}, \quad \gamma^g > \frac{\omega\|\alpha\|}{2} + \frac{(\beta^g)^2}{4(\beta^g - \frac{\omega\|\alpha\|}{2})}.$$

Then, $V(u,s)$ is a Lyapunov function, and (u^*, s^*) is globally asymptotically stable.

Targeted Drug Intervention



Let $z^q(t)$ be the control input targeting gene q.

$$\frac{du^g}{dt} = \alpha^g \underbrace{\frac{\kappa + \sum_{p\neq q}^{n_g} W_{gp}^{+} s^p(t) + z^q(t) W_{gq}^{+} s^q(t)}{\kappa + \sum_{p=1}^{n_g} W_{gp}^{-} s^p(t)}}_{:=R_g^{\circ}(z^q,s)} - \beta^g u^g(t),$$

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

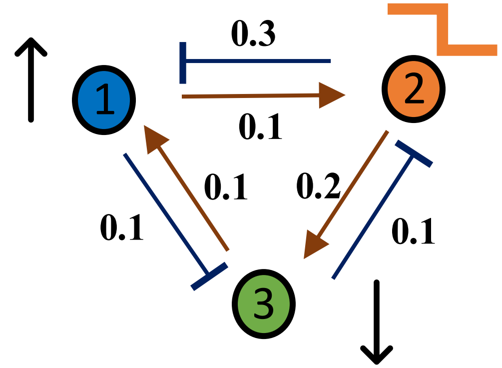
Formulate the drug intervention as a minimum time optimal control problem:

$$\begin{aligned} &\min_{z^q} \int_0^T 1 \; \mathrm{d}t \\ &\text{s.t. } \dot{u} = \alpha R^{\circ}(z^q, s) - \beta u, \\ &\qquad \dot{s} = \beta u - \gamma s, \\ &\qquad u(0) = u_0, \quad s(0) = s_0, \quad s(T) = s_f, \\ &\qquad z^q(t) \in \mathbf{U}, \;\; \forall t \in [0, T]. \end{aligned}$$

Exemplary Drug Intervention (I)

$$\frac{du^g}{dt} = \alpha^g \frac{\kappa + \sum_{q=1}^{n_g} W_{gq}^{+} s^q(t)}{\kappa + \sum_{q=1}^{n_g} W_{gq}^{-} s^q(t)} - \beta^g u^g(t),$$

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

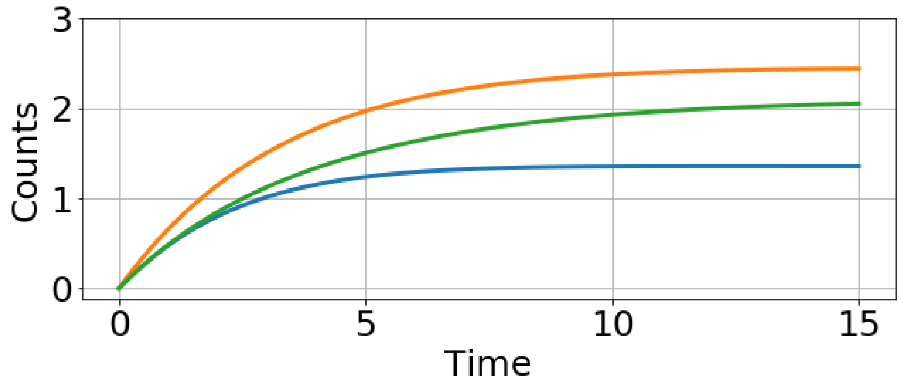


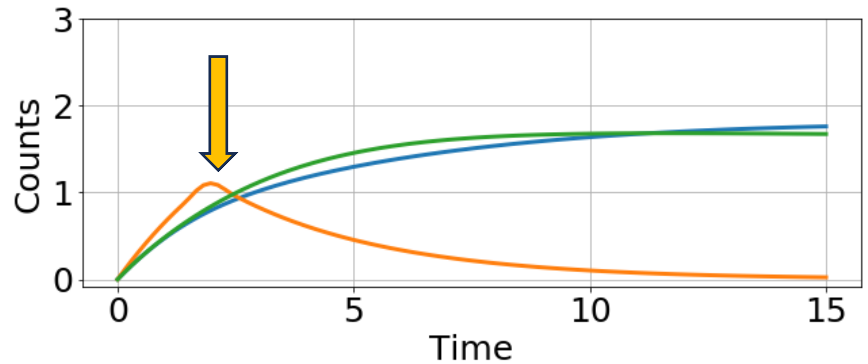
GRN

No intervention

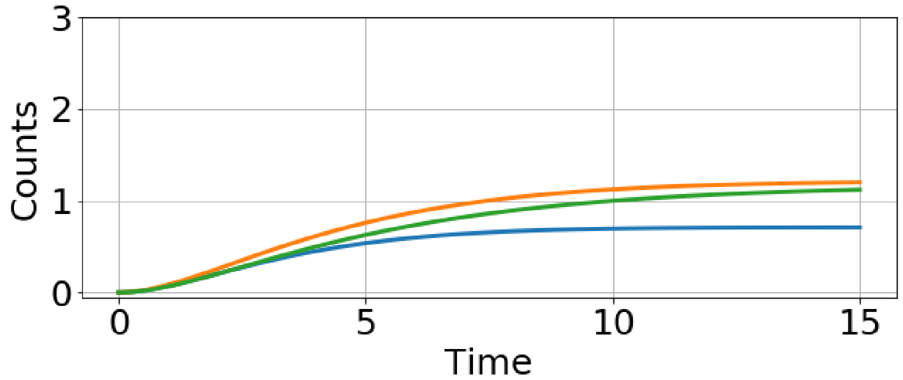
Knock out gene 2 at time t=2

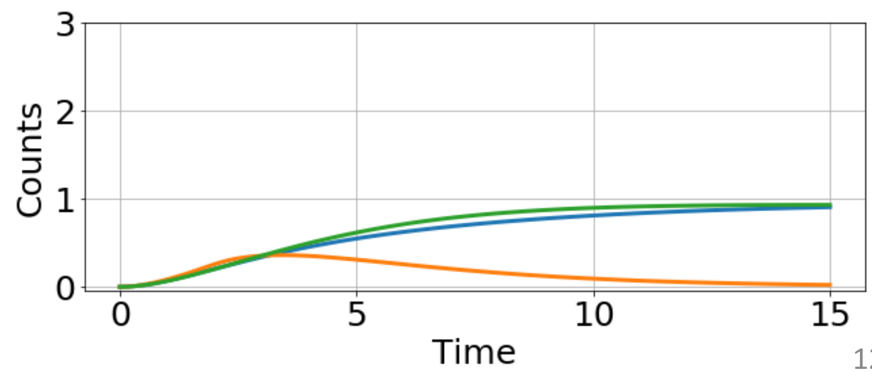
Unspliced $u(t)$





Spliced $s(t)$

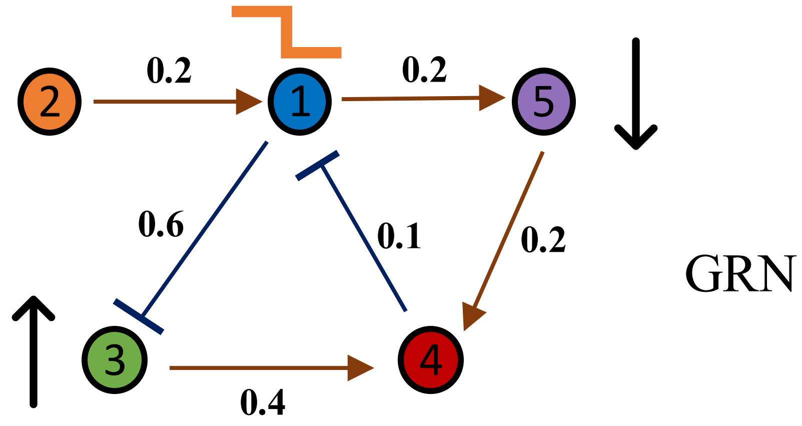




Exemplary Drug Intervention (II)

$$\frac{du^g}{dt} = \alpha^g \, \frac{\kappa + \sum_{q=1}^{n_g} W_{gq}^{+} s^q(t)}{\kappa + \sum_{q=1}^{n_g} W_{gq}^{-} s^q(t)} - \beta^g u^g(t),$$

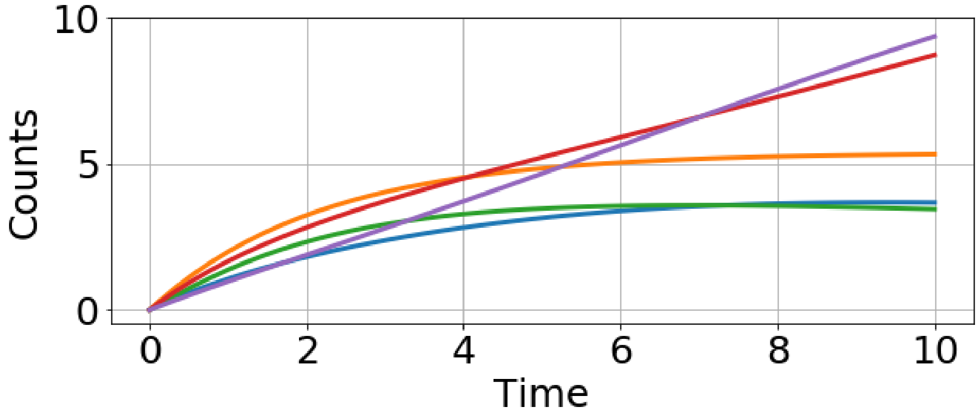
$$\frac{ds^g}{dt} = \beta^g u^g(t) - \gamma^g s^g(t).$$

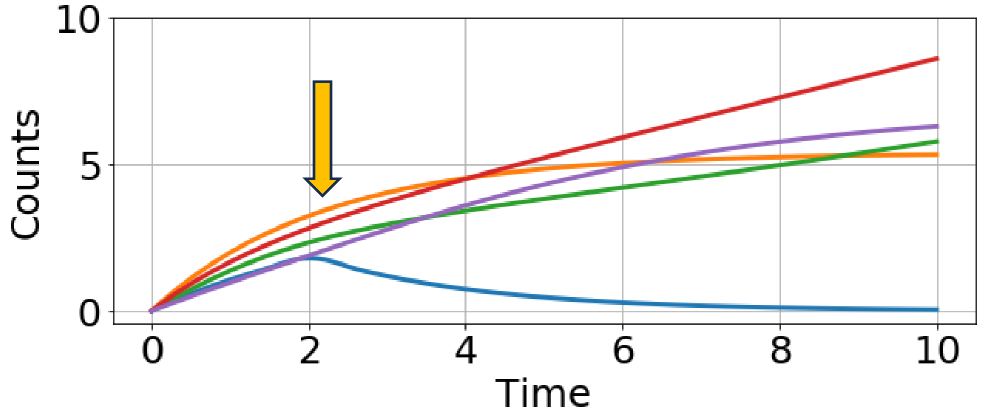


No intervention

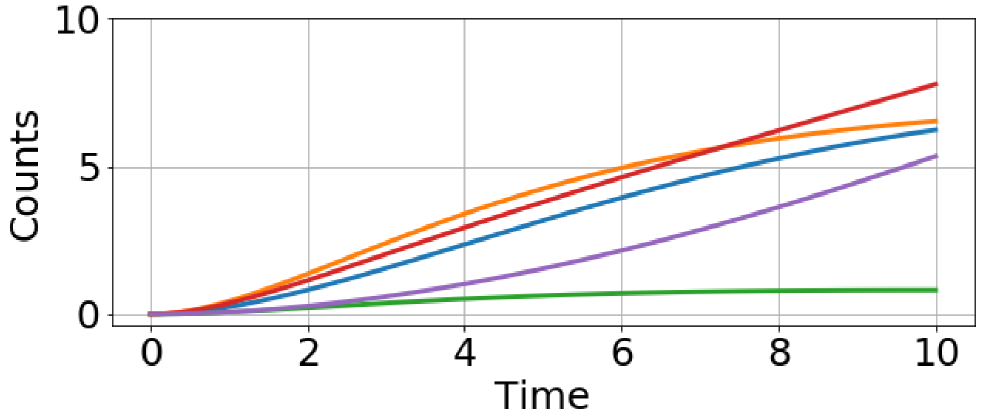
Knock out gene 1 at time t=2

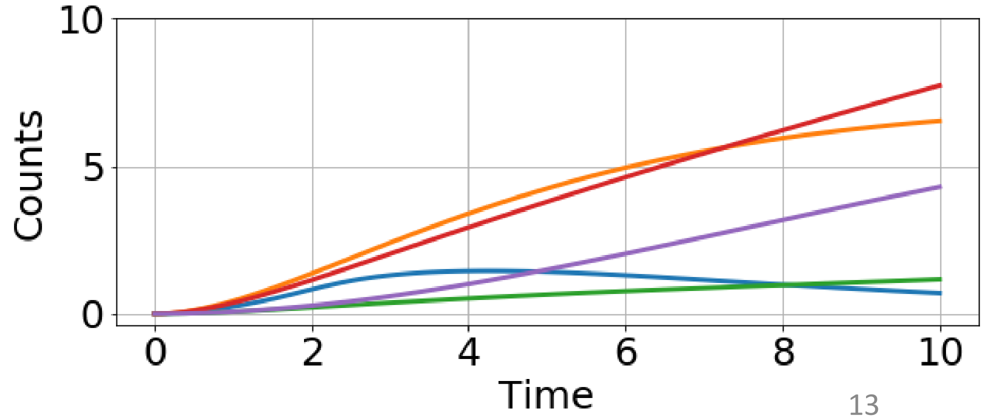
Unspliced $u(t)$





Spliced $s(t)$





Future Directions (in the full manuscript)

- Incorporate cell-to-cell interaction via spatial transcriptomics

$$\frac{du_i^g}{dt} = \alpha_i^g \frac{\kappa + \sum_{q=1}^{n_g} W_{gq}^{+} s_i^q(t)}{\kappa + \sum_{q=1}^{n_g} W_{gq}^{-} s_i^q(t)} - \beta_i^g u_i^g(t),$$

$$\frac{ds_i^g}{dt} = \beta_i^g u_i^g(t) - \gamma_i^g s_i^g(t) + \frac{c}{n_c} \sum_{j=1}^{n_c} a_{ij} \left(s_j^g(t) - s_i^g(t) \right)$$

- Examine how drug interventions may affect safety liability genes and design targeted drug intervention as controlled system.

Thank you !

boyahou2@illinois.edu

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