Mathematical Modelling of Genetic Network for Regulating the Fate Determination of Hematopoietic Stem Cells

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About me

- 2016 - B.Comm. in Financial and Insurance Mathematics, Monash Business School, Monash University
- 2017 - B.S.(Honours) in Probability and Statistics, School of Mathematics, Monash University
  - Research topic on probability theory and large deviation principle
- 2022 - Ph.D. in Applied Mathematics, School of Mathematics, Monash University
  - Research interest is Mathematical Biology, Stochastic Modelling and Dynamical Systems Theory
  - Developed mathematical modelling and inference algorithms to investigate the dynamical mechanisms of genetic regulation for cell fate determination
- 2022 - PostDoc/Lecturer at Department of Molecular and Cell Biology, James Cook University
  - Joined A/Prof. Ulf Schmitz's team
  - Continue work on mathematical modelling of biological systems
  - Member of Australian Mathematical Society

Introduction

Why Mathematical Biology?

Introduction

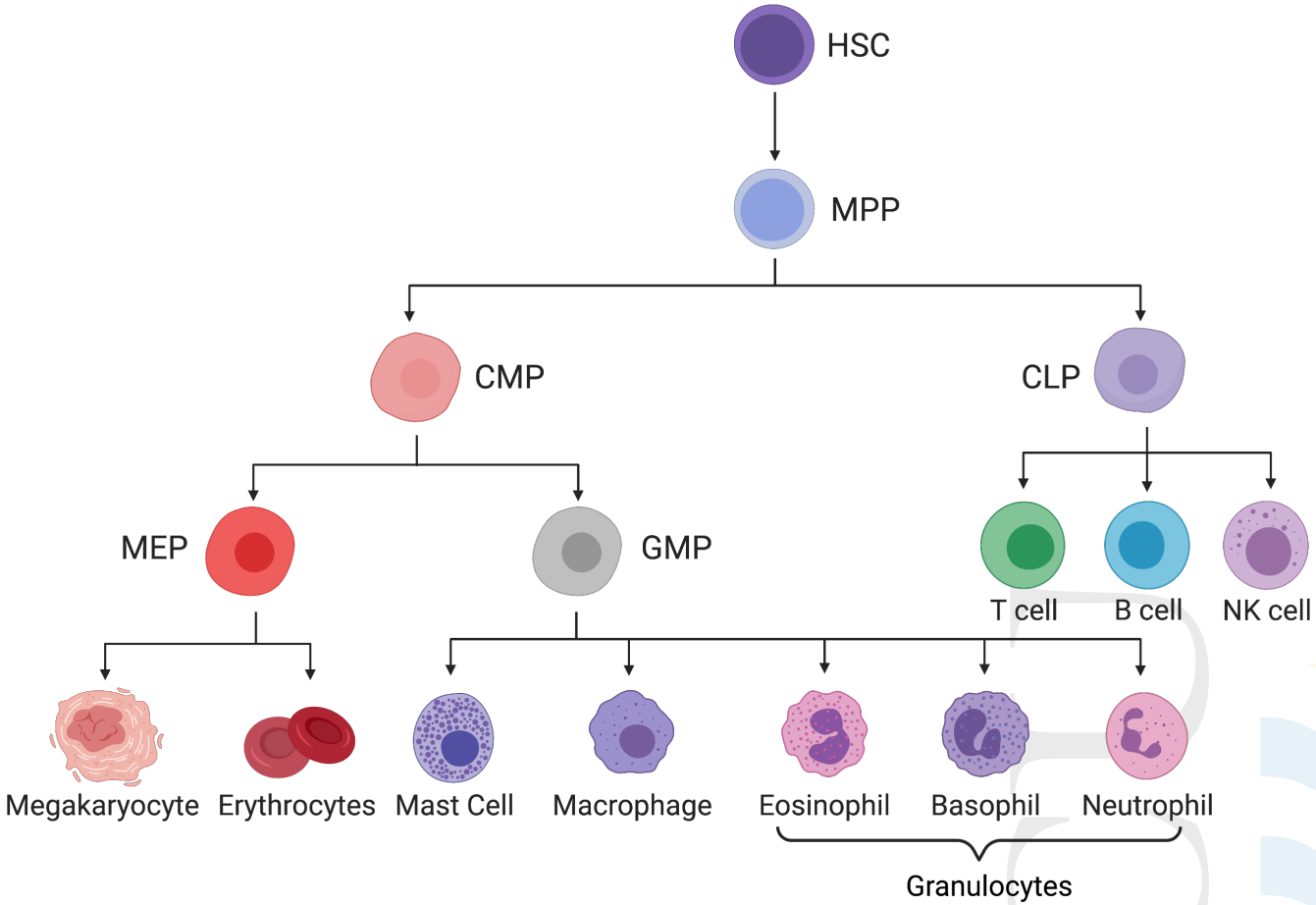

Figure 1: Diagram of the developmental process of hematopoietic stem cell. Created with BioRender.com.

Classification of states

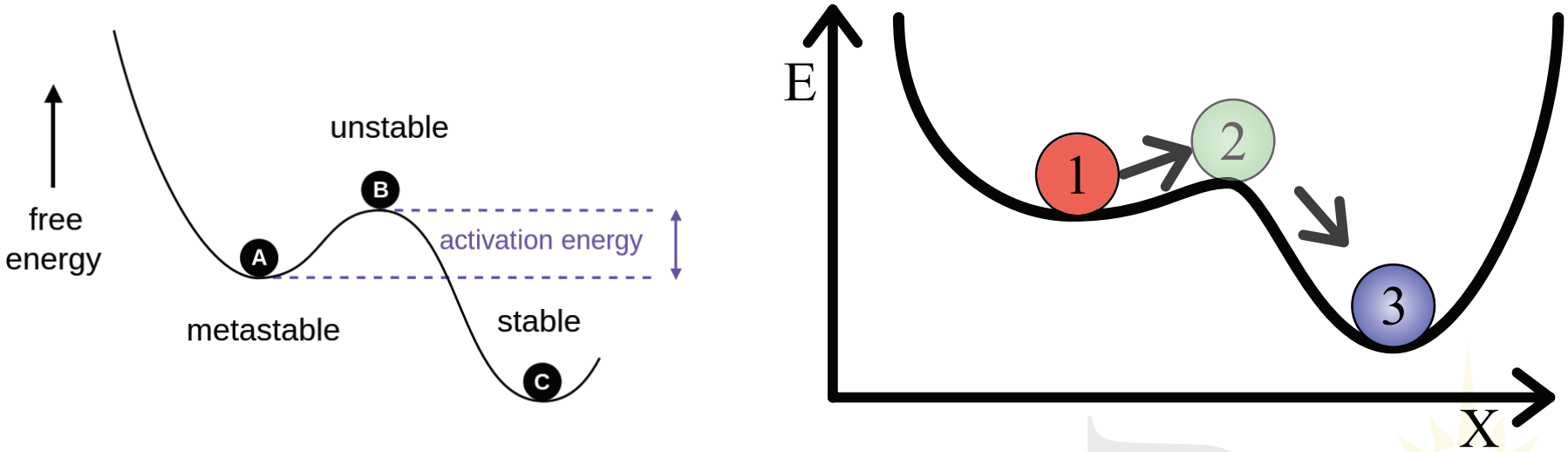

Figure 2: Thermodynamic Stability of Matter in a System.
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Georg Wiora (Dr. Schorsch), CC BY-SA 3.0 via Wikimedia Commons

Development of sequencing technologies

- What cell states exist?
- Where are they located?
- How are they related?

The central strategies of regenerative medicine

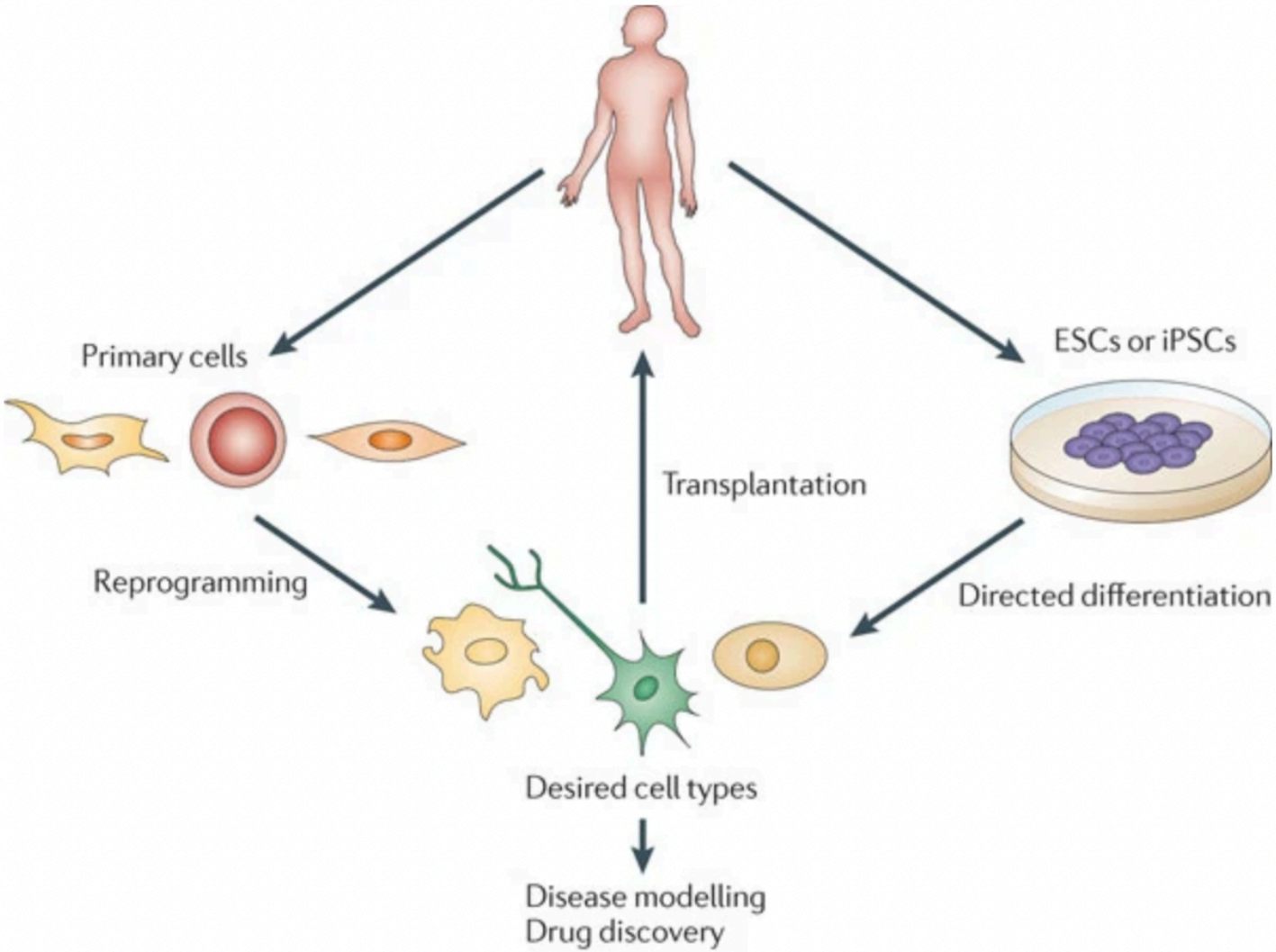


Figure 3: Cohen, D., Melton, D. Turning straw into gold: directing cell fate for regenerative medicine. Nat Rev Genet 12, 243–252 (2011)

Motivation

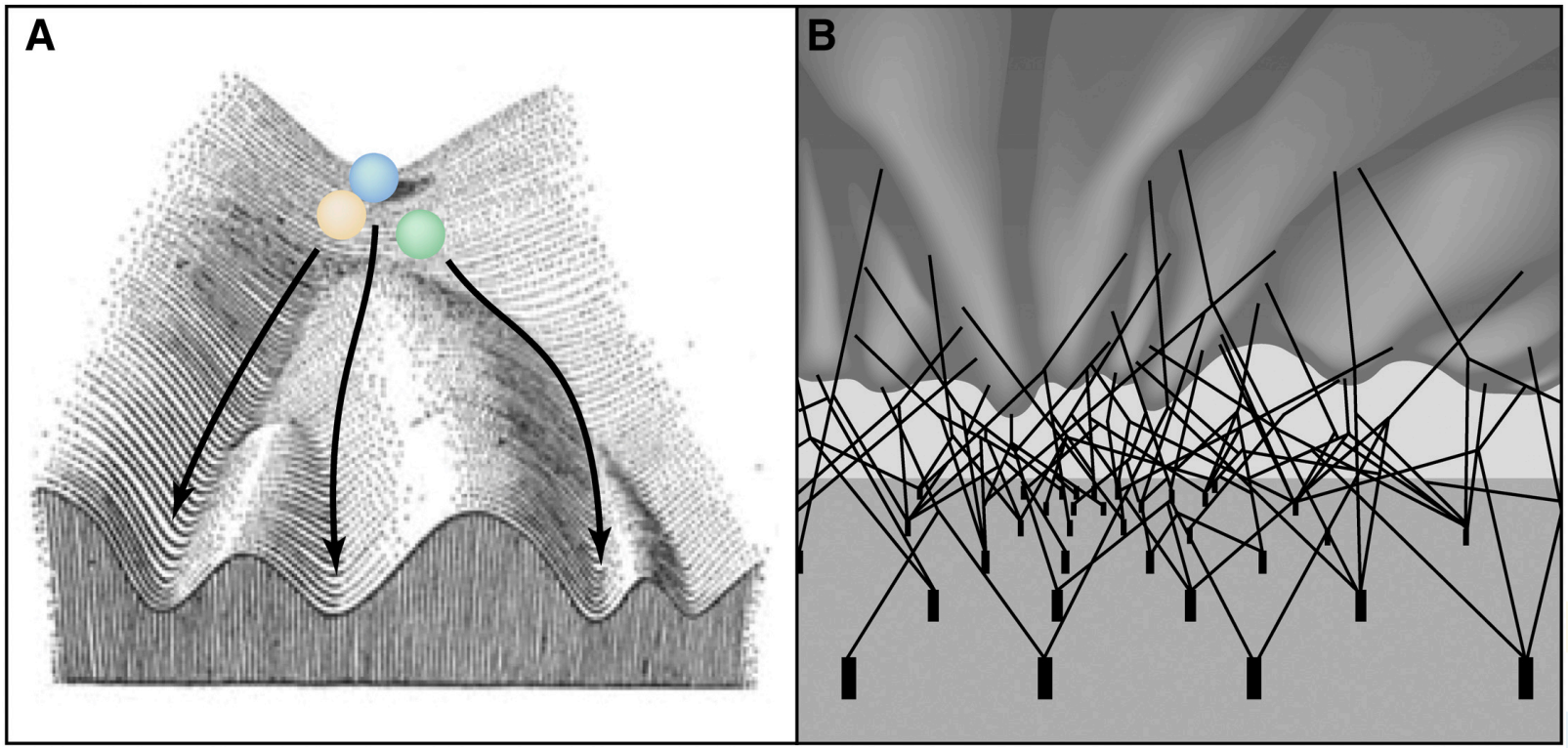


Figure 4: Rajagopal, J., and Stanger, B. Z. (2016). Plasticity in the adult: how should the Waddington diagram be applied to regenerating tissues? Developmental cell, 36(2), 133-137.

Background

A multistable system is a dynamic system with multiple stable states. Multistability is a common dynamic behaviour in the biological system. For example,

- biochemical reactions
- cell signalling systems
- genetic regulatory networks (GRN)

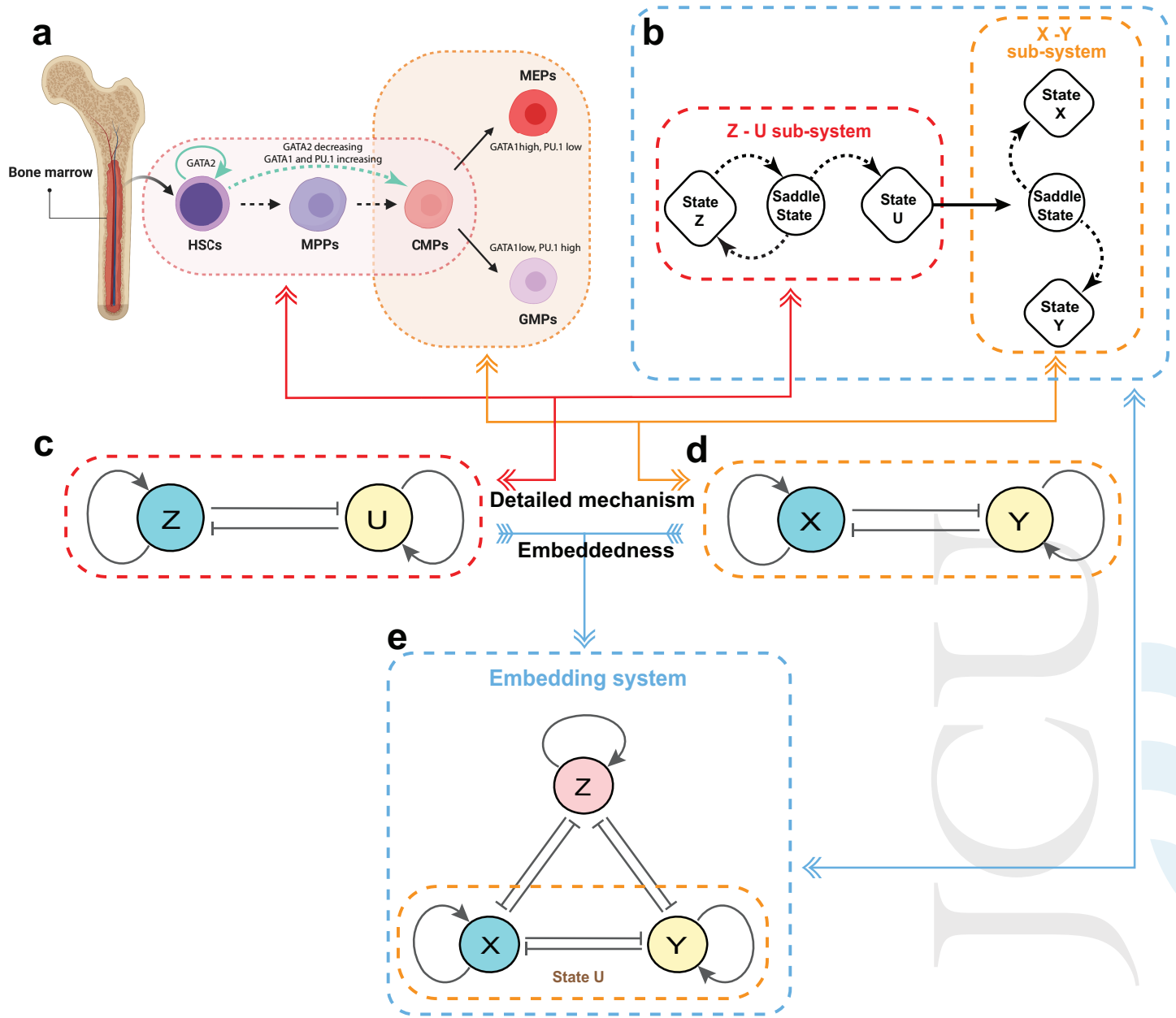
For the system of cell development, an ideal system should be able to put cells into multiple distinct, and stable, cell states.

Assumption

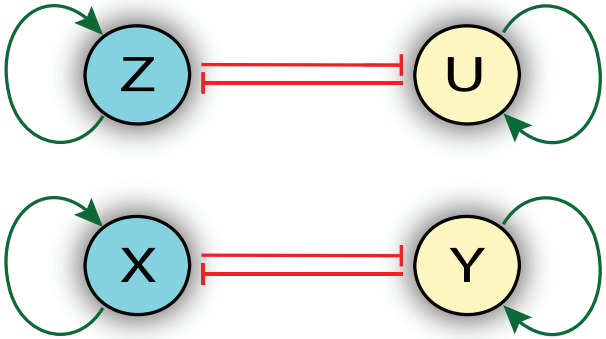
Assumption 1

In this study, we assume that a multistable system makes a series of binary choices about the selection of multiple lineage pathways.

Embedding method in HSC genetic regulatory network



Modelling of two-nodes GRNs I



Formulation of Z-U sub-system and X-Y sub-system

$$\frac{dz}{dt} = \mathcal{F}_1(z, u, \mathbf{\Theta}_1, t) = \frac{a_1 z}{1 + b_1 z} \frac{1}{1 + b_2 u} - k_1 z,$$
$$\frac{du}{dt} = \mathcal{F}_2(z, u, \mathbf{\Theta}_1, t) = \frac{c_1 u}{1 + d_1 u} \frac{1}{1 + d_2 z} - k_2 u. \quad (1)$$

$$\frac{dx}{dt} = \mathcal{G}_1(x, y, \mathbf{\Theta}_2, t) = \frac{\alpha_1 x}{1 + \beta_1 x} \frac{1}{1 + \beta_2 y} - k_3 x,$$
$$\frac{dy}{dt} = \mathcal{G}_2(x, y, \mathbf{\Theta}_2, t) = \frac{\gamma_1 y}{1 + \sigma_1 y} \frac{1}{1 + \sigma_2 x} - k_4 y. \quad (2)$$

Biological facts used in the model

- Three candidate genes - *GATA1, GATA2, PU.1*
- Experimental studies suggested that *GATA2* and *GATA1* sequentially bind the same cis-elements, which is referred to as GATA-switching. This is the main driver of hematopoiesis. During the process of GATA-switching, the displacement of *GATA2* and binding of *GATA1* at the same *cis-element* will lead cells to leave the HSCs state.
- After *GATA2* unbinding, the dynamical competition of *GATA1-PU.1* will decide the final cell fate.

Simulation results for two-node models I

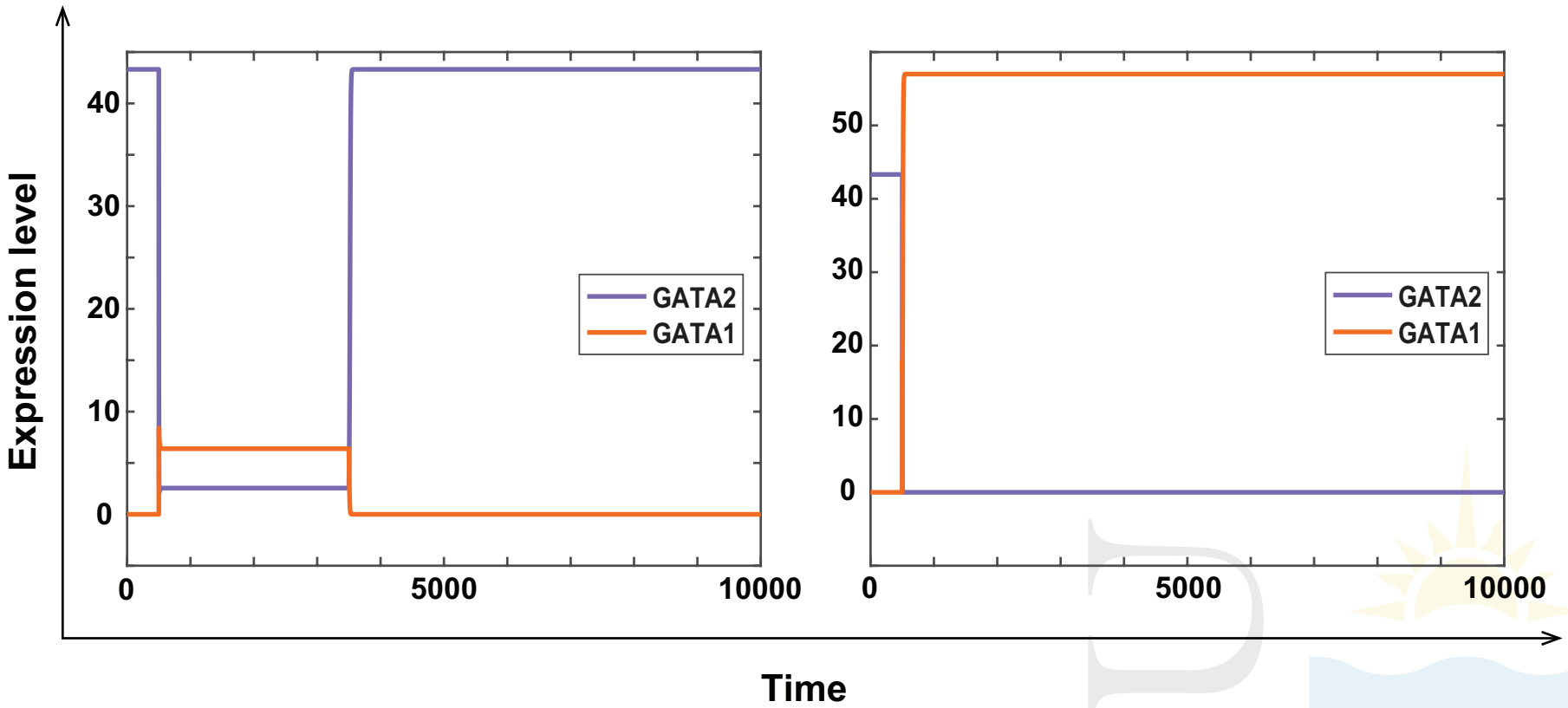


Figure 5: Left panel: An unsuccessful switching due to the displacement of *GATA2* is not enough for cells to leave the HSCs state (Z state); Right panel: A successful switching with enough displacement of *GATA2*. Cells leave the HSCs state and enter the U state.

Simulation results for two-node models II

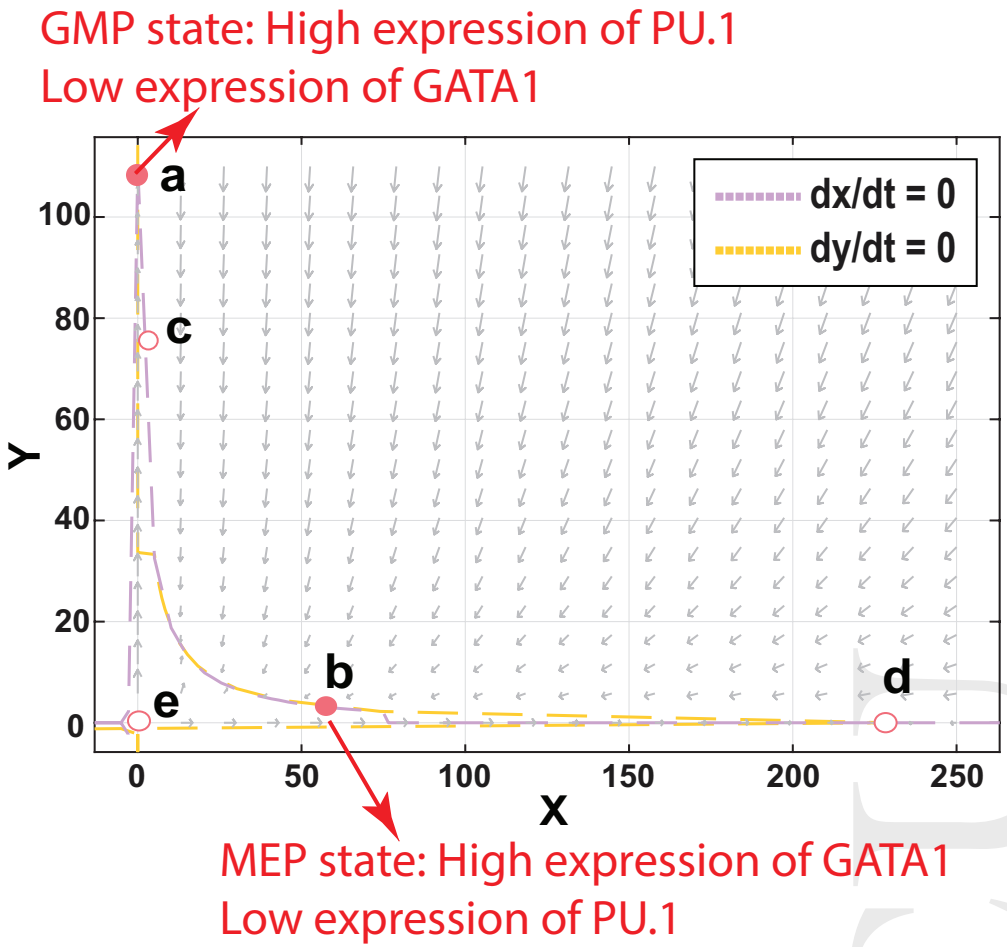
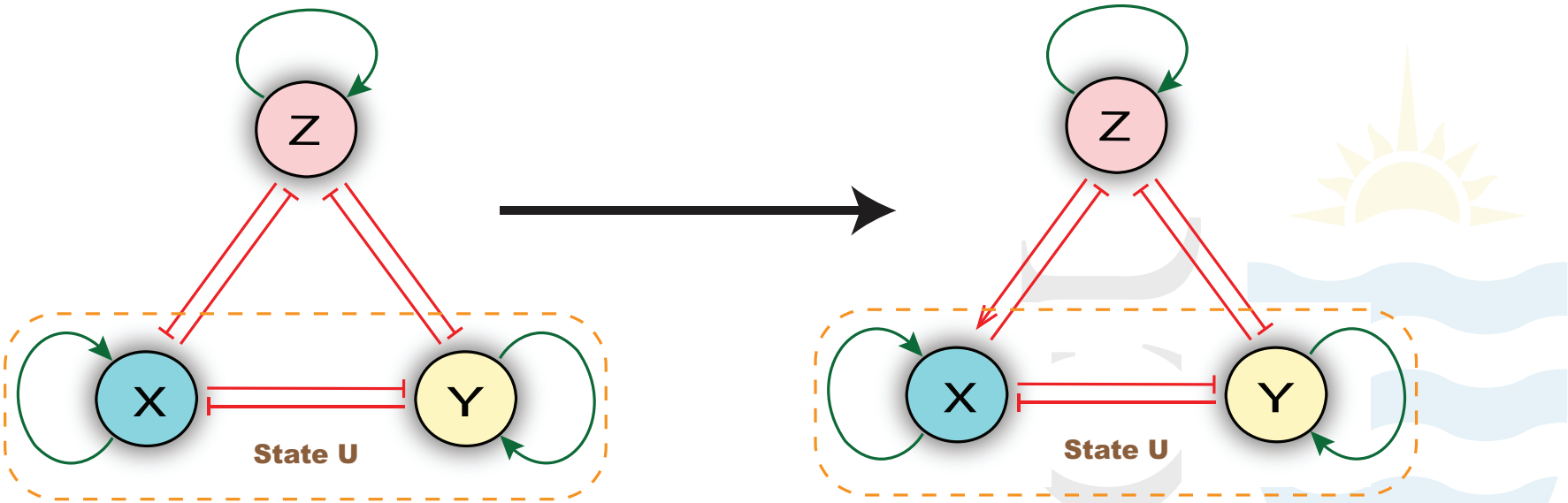


Figure 6: Phase plane of the *GATA1-PU.1* module shows the bistable property of the proposed model, where a and b are stable states

Modelling of the three-nodes embedded GRN I

Biological facts we considered when embedding two sub-systems

- experimental studies suggest that *GATA2* moderately stimulates the expression of gene *GATA1*.
- Zero basal gene expression makes no sense.



Modelling of the three-nodes embedded GRN II

Therefore, our final modified embedded model is

Modified three-nodes GRN with GATA switching

$$\begin{aligned}
\frac{dx}{dt} &= \frac{\alpha_0 + \alpha_1 x}{1+\beta_1 x}\frac{1}{1+\beta_2 y}\frac{1+d^* z}{1+d_2 z} - k_3 x + \psi k^* z, \\
\frac{dy}{dt} &= \frac{\gamma_0 + \gamma_1 y}{1+\sigma_1 y}\frac{1}{1+\sigma_2 x}\frac{1}{1+d_2 z} - k_4 y, \\
\frac{dz}{dt} &= \frac{a_0 + a_1 z}{1+b_1 z}\frac{1}{1+b_2(x+y)} - k_1 z - k^* z.
\end{aligned} \tag{3}$$

Modelling of the three-nodes embedded GRN III

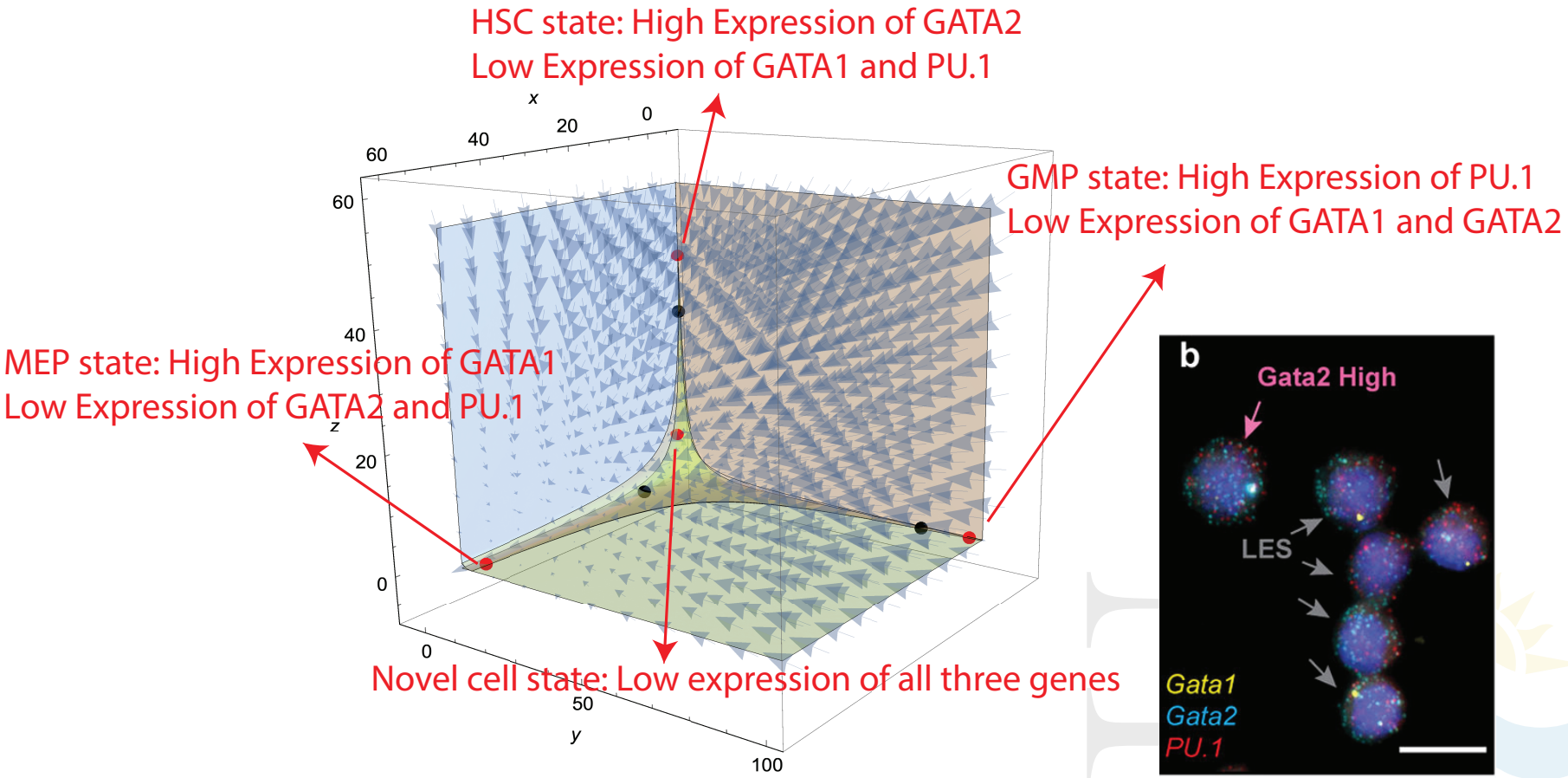
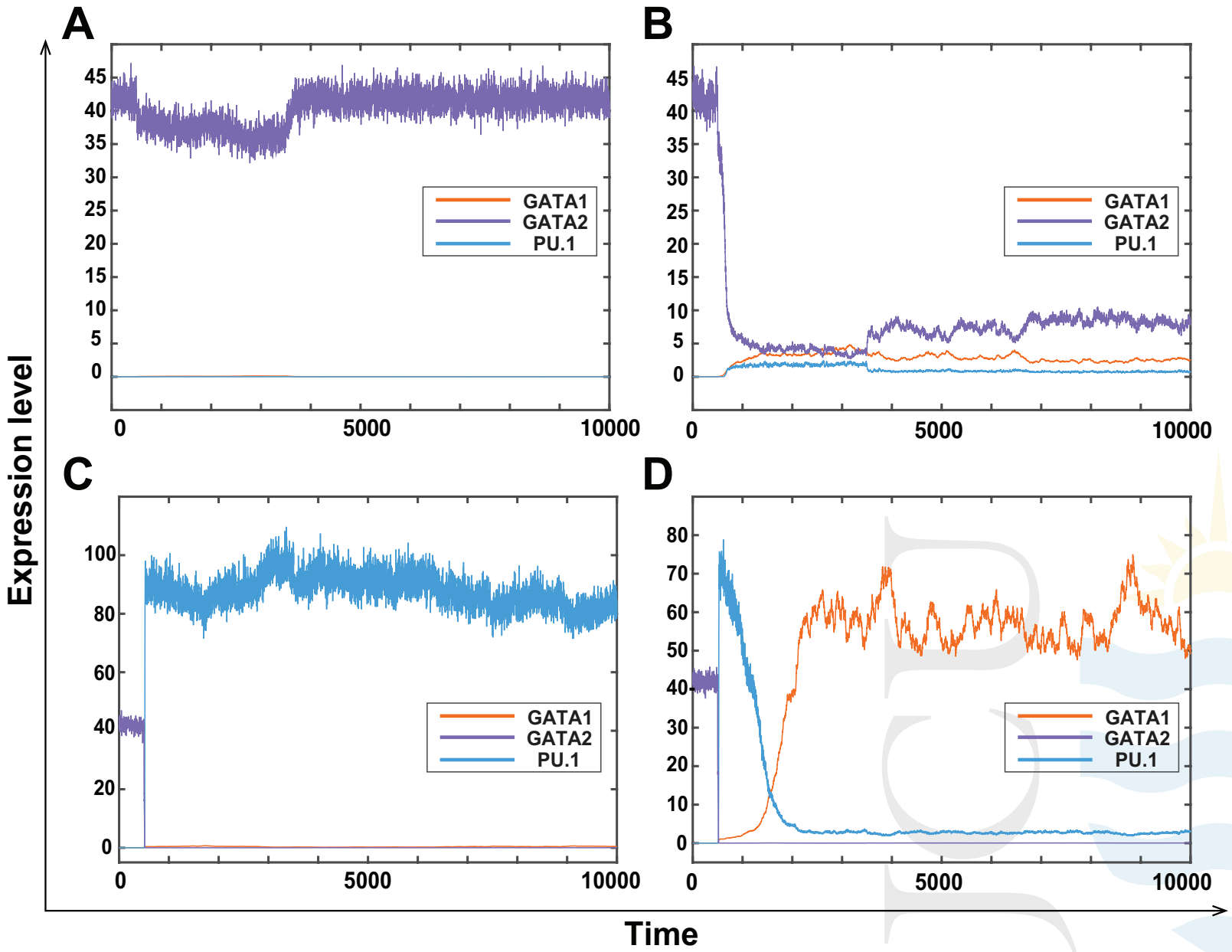


Figure 7: The 3D phase portrait of the modified embedded system.
Figure reference: Wheat JC et al. Single-molecule imaging of transcription dynamics in somatic stem cells. Nature. 2020 Jul;583(7816):431-436.

Stochastic dynamics

$$
\begin{aligned}
dX(t) &= \left[\frac{\alpha_0+\alpha_1 X(t)}{1+\beta_1 X(t)}\frac{1}{1+\beta_2 Y(t)}\frac{1}{1+d_2 Z(t)} - k_3 X(t) + \psi k^* Z(t)\right] dt \\
&\quad + \omega_1 [k_3 X(t) + \psi k^* Z(t)] dW_t^1, \\
dY(t) &= \left[(\frac{\gamma_0+\gamma_1 Y(t)}{1+\sigma_1 Y(t)}\frac{1}{1+\sigma_2 X(t)}\frac{1}{1+d_2 Z(t)} - k_4 Y(t)\right] dt \\
&\quad + \omega_2 k_4 Y(t) dW_t^2, \\
dZ(t) &= \left[(\frac{a_0+a_1 Z(t)}{1+b_1 Z(t)}\frac{1}{1+b_2(\mu X(t)+\delta Y(t))} - k_1 Z(t) - k^* Z(t)\right] dt \\
&\quad + \omega_3 (k_1+k^*) Z(t) dW_t^3.
\end{aligned}
\tag{4}
$$

Stochastic dynamics II



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- Tiangang Cui

Thanks for listening!