Modeling Bistability in Stem and Multipotent Progenitor cells

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1. INTRODUCTION

The central dogma of molecular biology represents the flow of genetic information to form a functional product which a protein, from the most important molecules in cell biology DNA and RNA. The synthesis of protein is has two different phases: transcription and translation. Every protein has its own specificity and function, all the major life-critical processes in cells are performed by proteins [1].

Although the genetic information in all differentiated cells is the same, the set of genes expressed is different in each differentiated cell, the cells also undergo a number of environmental disturbances, requiring an appropriate spatio-temporal regulation of gene expression.

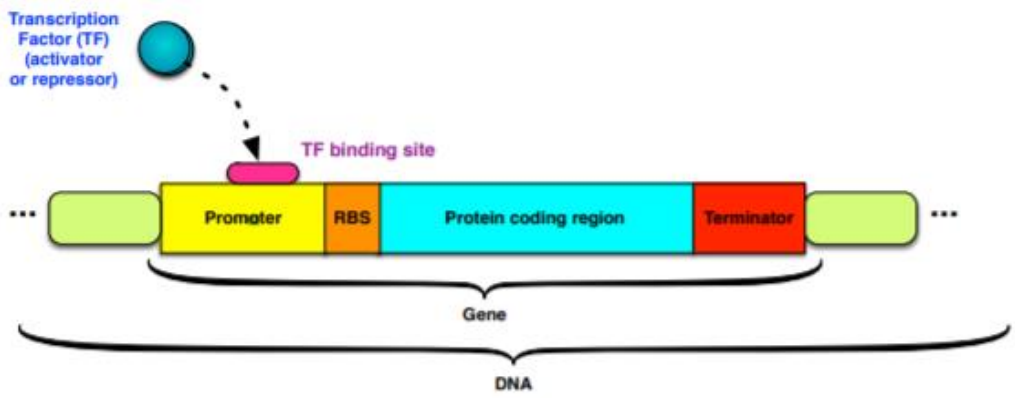

Fig1: Gene-transcription regulation [1]

At the transcription level, the expression of gene is controlled by specific proteins, which are known as transcription factors. The Auto-activation and Auto-inhibition occurs when the promoter of that particular gene is managed by the transcription factor that it encodes.

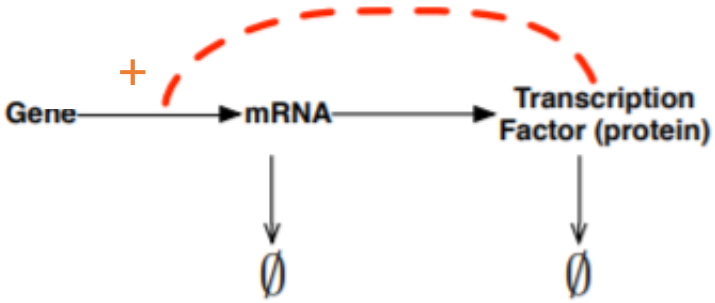

Fig2: Auto-activation and Auto-inhibition of gene expression [2]

Auto activation of gene expression can be expressed as a mathematical model, using ordinary differential equations with the help of the hill function.

$$\frac{dx}{dt} = k_1 \frac{y^n}{K^n + y^n} - d_1 x$$

$$\frac{dy}{dt} = k_2 x - d_2 y$$

where, x = mRNA, y = transcription factor (protein), k_1,k_2 are the maximal transcription rates, K is the repression coefficient, n is the Hill coefficient and $\frac{y^n}{K^n + y^n}$ $f^+(y)$ = is a monotonically increasing hill function, for auto-activation of transcription factor.

PROBLEM STATEMENT:

Stem cells can continuously differentiate and divide into different kinds of cells and tissues. It is a challenging issue to previously determine the factors that decide its fate. One way is through mathematical modeling. In this way, an appropriate model will help us overcome experimental challenges to determine the fate in stem cells and their differentiation. Hill function has been implemented previously [1] and has been successful in providing an efficient model in systems biology, gene switch modeling. Here the idea is to understand and implement the same for a particular progenitor cell whose fate is determined by two transcription factors that are auto-regulating and auto-activating. The transcription factors help in determining the lineage of the progenitor cell. PU.1 and GATA.1 are the two transcription factors that regulate the differentiation of a specific branch of blood cells granulocyte/macrophage lineage (WBC) or the lineage erythroid/megakaryocyte (RBC) (Fig 2). Appropriate modelling of these factors can be used to control stem cell development, thereby making it useful for several therapeutic applications. This will also help in quantifying intuitions to perform validation experiments and get an understanding of the dynamics of the system under question(cell biology).

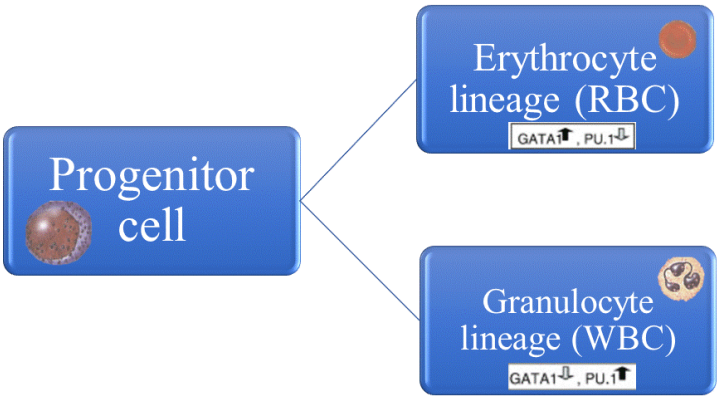

Fig 3: Lineages in the blood stem cell

2. METHODOLOGY:

2.1 SOLUTION OF THE DYNAMIC SYSTEM:

GATA.1 and PU.1 are the two transcription factors that control the lineage of the stem cell. They are auto-activating, one regulates the production of the other. Therefore, the Hill function with appropriate model parameters can be used to mathematically model the factors.

Mathematical model [2],

$$\frac{dx}{dt} = a_1 \frac{x^n}{\theta_{a1}^n + x^n} + b_1 \frac{\theta_{b1}^n}{\theta_{b1}^n + y^n} - k_1 x$$

$$\frac{dy}{dt} = a_2 \frac{y^n}{\theta_{a2}^n + y^n} + b_2 \frac{\theta_{b2}^n}{\theta_{b2}^n + x^n} - k_2 y$$

where, $a_1, a_2, k_1, k_2, b_1, b_2, n, \theta$ are non-negative parameters.

a_1, a_2 – auto-regulation parameter.

b_1, b_2 – cross-inhibition parameter.

k_1, k_2 – rate of first order deactivation.

θ – threshold of the functions.

n – Hill coefficient.

The first term in the differential equation represents auto-stimulation activity, second term represents cross-inhibition activity and third term represents unregulated decay of activity.

The system of ODE were solved using MATLAB ode45 function.

The graphs (Fig 4a-4b) obtained for the differentiation of the stem cell for different parameters - solution for the ODEs.

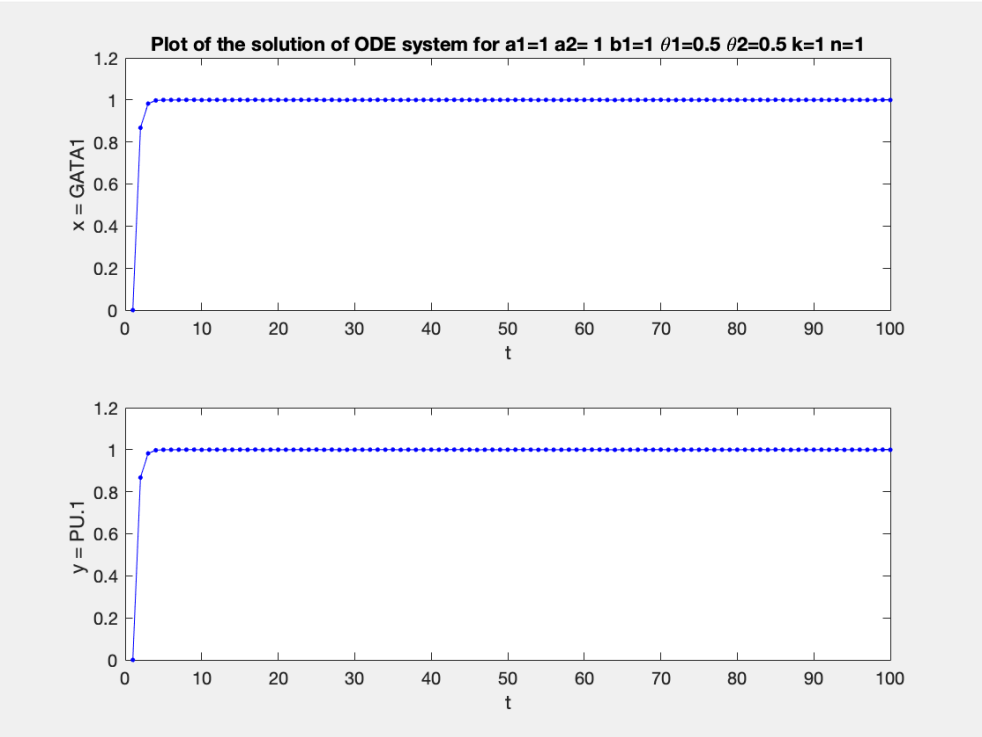

Fig4a Solution of the ODEs

Here (Fig4a), we observe the auto-regulatory functions of the two factors. The concentration of [GATA.1] and [PU.1] increases at the same time and they become constant after a point. We observe a transient increase and see it reach a steady-state.

To observe how auto-regulatory parameters affect the system, we take the condition a2>a1.

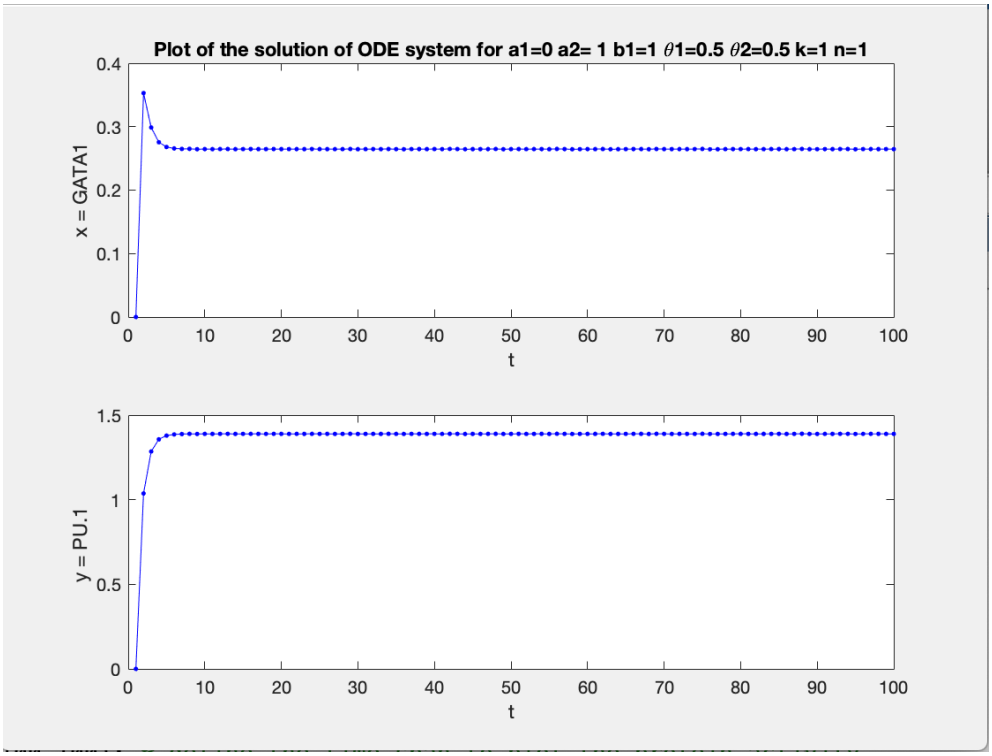

Fig4b Solution of the ODEs

In Fig 4b, the concentration level of [GATA.1] does not improve overtime and we observe the [PU.1] expression is dominating in the fate of the progenitor cell.

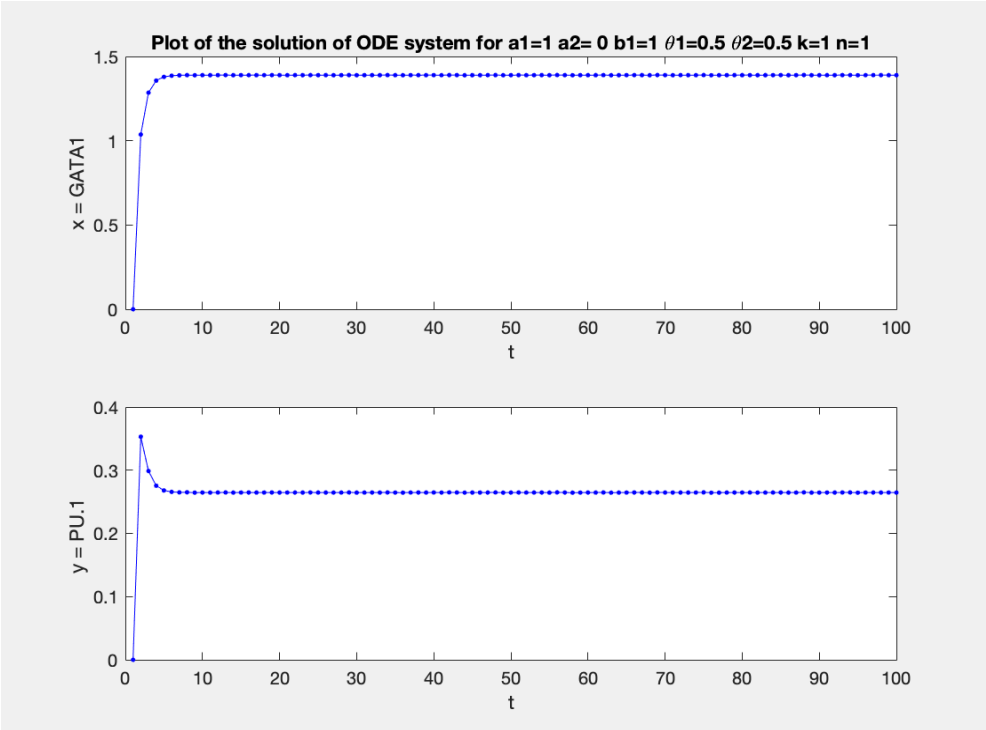

Fig4c Solution of the ODEs

We observe similar effects when a1>a2. [PU.1] domination becomes null and we see only [GATA.1] increase over the time axis.

The cross-inhibition parameters b1 and b2, inhibits the expression level by the parameter provided.

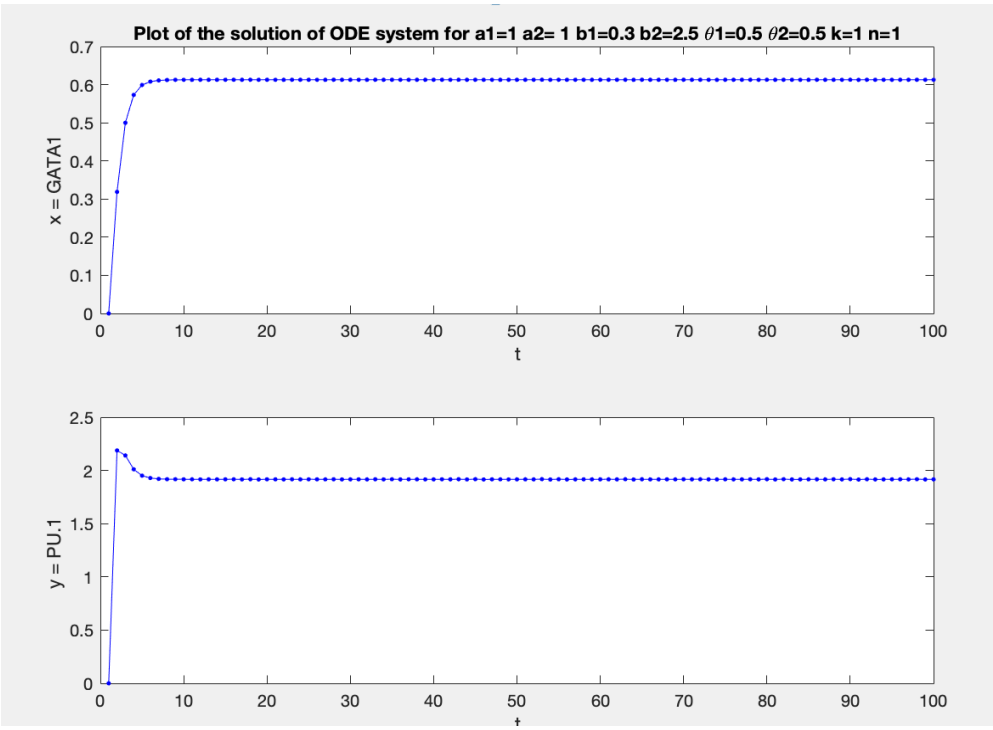

Fig 4d Solution for the ODEs

For b1 = 0.3, the concentration of [GATA.1] is decreased when compared to b1 = 1 (when decreased). For b= 2.5, the concentration of [PU.1] is more when compared to b=1(when increased).

2.2 BIFURCATION ANALYSIS AND VECTOR PLOTS:

Bifurcation analysis is used to study the behavior of the biological systems modeled as dynamical systems, it describes how small changes in an input parameter can cause huge qualitative changes or bifurcations is the behavior of the system. The parameter ‘k’ defining first order deactivation in the system helps understand the behavior of the transcription factors.

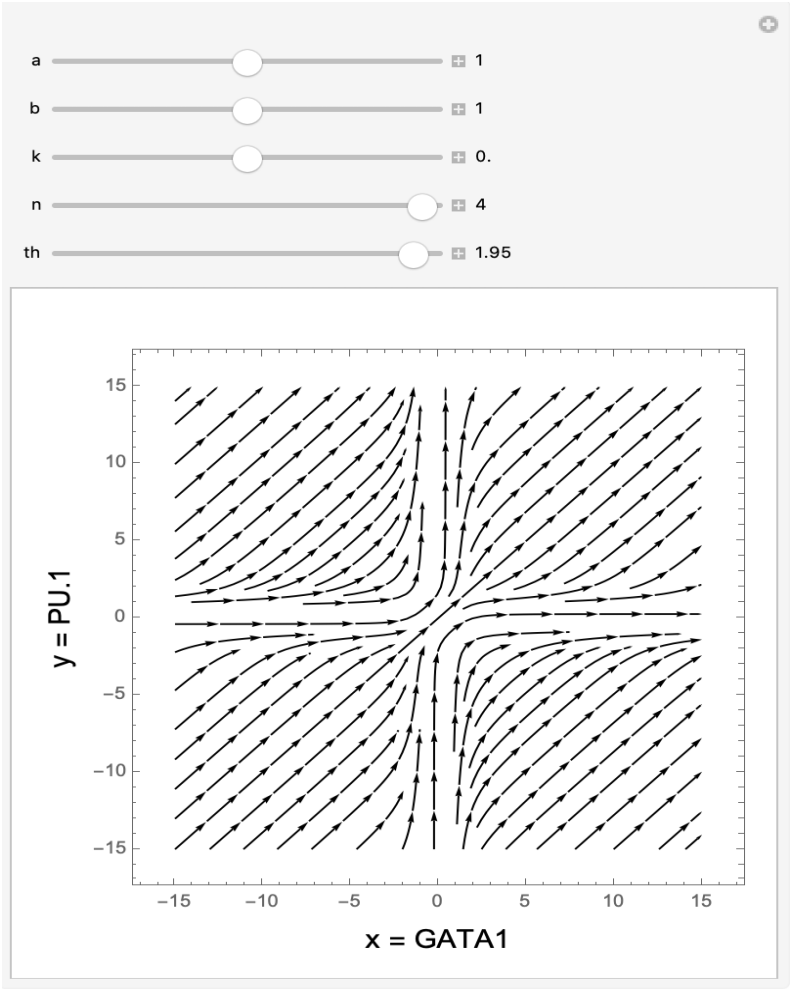

Fig 5a Vector plot (k=0)

In this case: for **k=0,** we observe an improper node bifurcation at the critical point. Here we will observe two attractor basins, one towards [PU.1] and other towards the [GATA.1] basin. Both transcription factors are dependent on each other depiction autoregulation and auto-activation functions in the dynamic system.

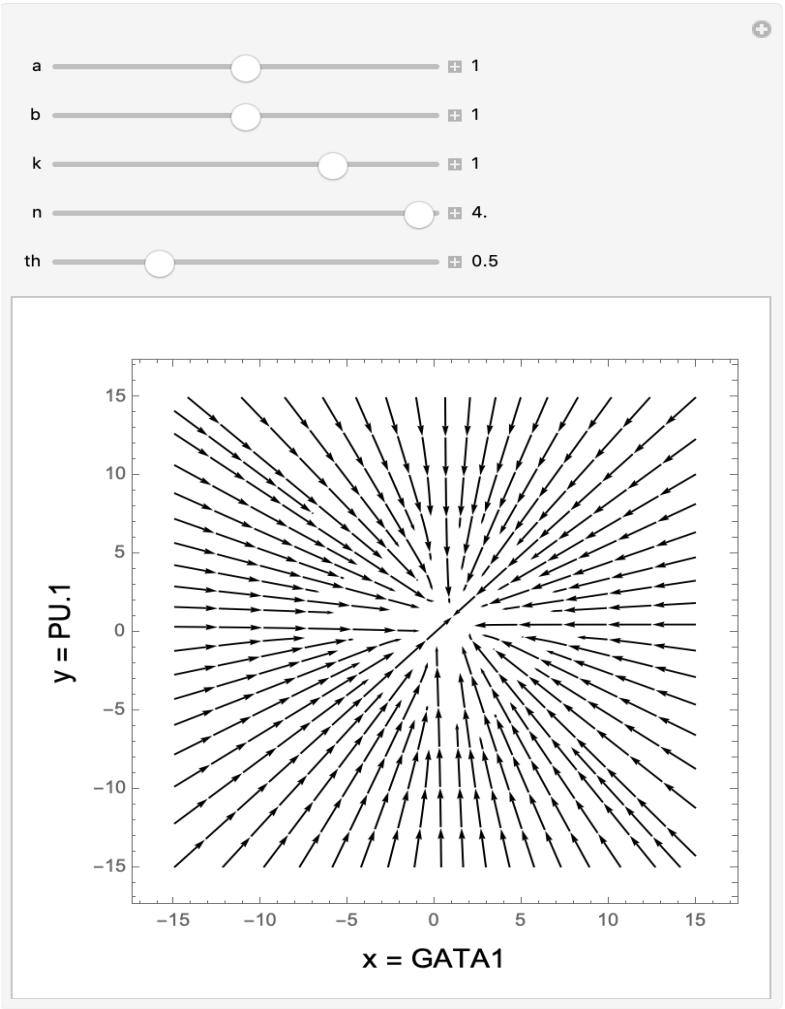

Fig 5b: Vector plots (k>0)

Here, **k>0** we observe a stable bifurcation at the critical point.

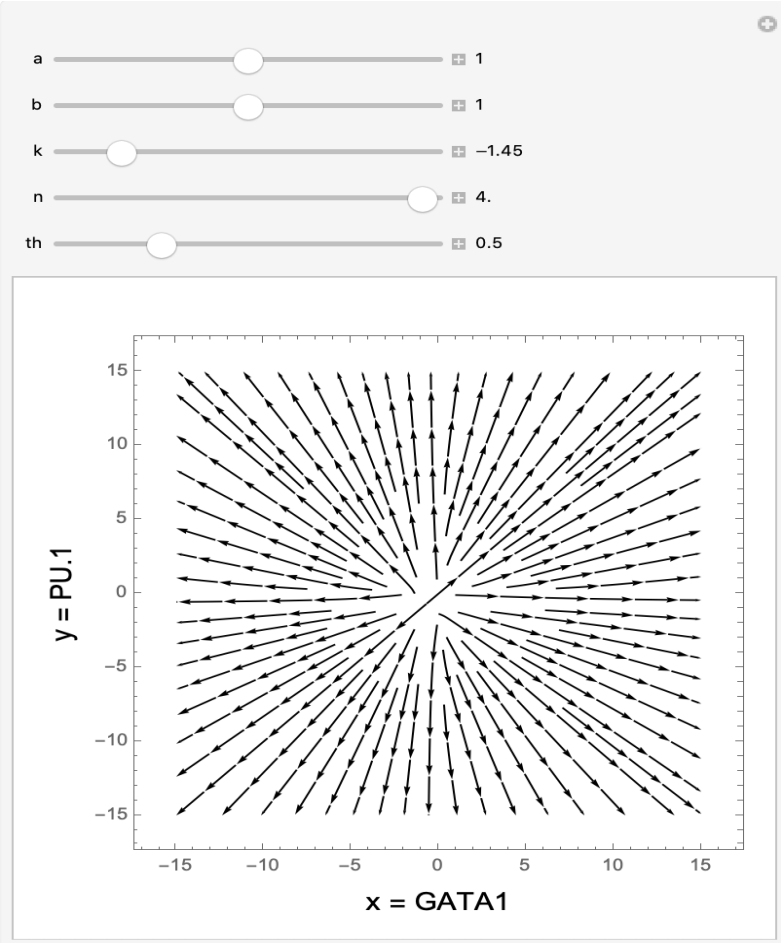

Fig 5c: Vector plots (k<0)

And for **k<0,** the system is observed to have unstable node bifurcation.

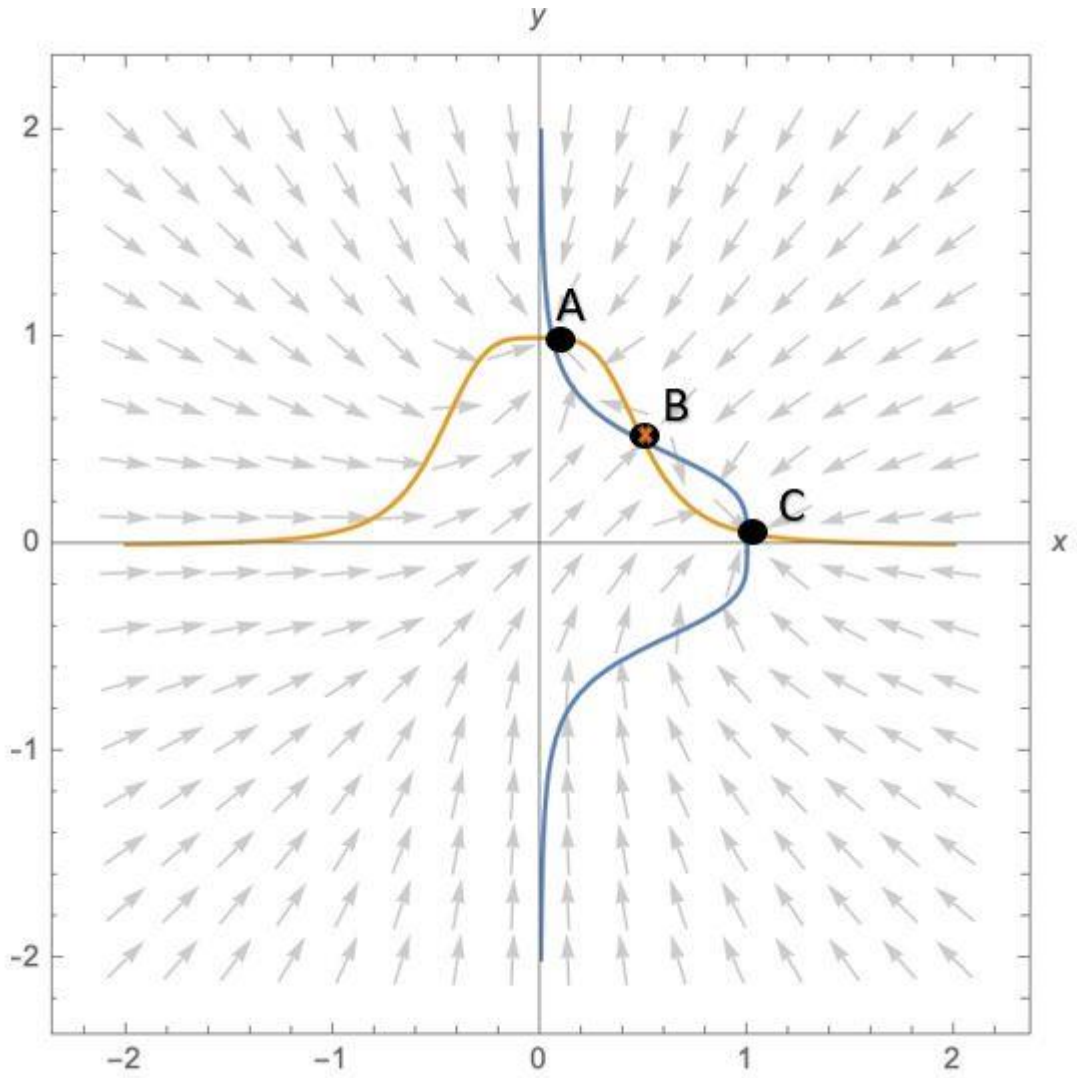

Fig6: Vector plots showing the stable and unstable points.

In this plot, we observe how the vector plot behaves with nullclines, the differentiation of the equation is equal to 0 ($\frac{dx}{dt} = 0$). The contour plot and the vector plot were overlapped and this provides us an explanation in the shift of the direction of the vectors in the system at the points where two nullclines meet. The points A and C show a stable point in the system. And point B is a saddle point. As the arrows converge at point B, they move apart towards A or C.

3. SUMMARY:

In this project, we have used ODEs to model the differentiation of stem cells, to determine the lineage of the cell. The modelling was done using Hill function, which is a very common function that has been used to model dynamical systems. The ODEs were solved using MATLAB's ode45 function and the Vector and Bifurcation analysis was done in Mathematica.

Both teammates Harshitha Govindaraju (hg293) and Sumana Ramanathan (sr1423) contributed equally in all parts of the project.

References:

1. Stan, P. G.-B. (2019). Modelling in Biology.
2. Huang, S., et al. (2007). "Bifurcation dynamics in lineage-commitment in bipotent progenitor cells." Dev Biol 305(2): 695-713.
3. Schiesser, W. E. Differential Equation Analysis in Biomedical Science and Engineering : Ordinary Differential Equation Applications with R . Hoboken, New Jersey: Wiley; 2014.