Biochemical Switches

CS304 Non-Linear Science Project Report

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1 Abstract

Dynamical processes within living cell are based on biochemical reactions. Gene regulation and biological pattern formation are a few such examples. Specially in gene regulation, the biological functionality is strongly connected to the qualitative dynamical behaviour of the network.
There have been various attempts at modeling these biological phenomena, cellular automata being one such approach. However, modeling using the "game of life" or the "one dimensional cell automaton" lack biological relevance[1]. And hence, if one wished to understand these patterns, they must use a different model.
This paper presents the analysis of a non-linear dynamics approach to one such model, proposed by Lewis et al.[4] in 1977, using a single element biochemical switch.

2 Introduction

A biochemical switch model takes into consideration a gene, which is activated by a bio-chemical signal substance. To put it into perspective, the gene may be inactive to start with but it can be turned to its "on" mode to produce melanin pigments or other gene products when the concentration exceeds a certain threshold.

There is a linear degradation of the gene at a constant rate. The production of the gene is stimulated by the concentration of the bio-chemical signal substance at a constant rate, and by an autocatalytic or positive feedback process which brings in non-linearity in the system.

The equation:

$$\frac{dg}{dt} = k_1 s_o - k_2 g + \frac{k_3 g^2}{{k_4}^2 + g^2} \tag{1}$$

Where

- g is the concentration of the gene (a high concentration means that the gene is "activated")
- s_o is the initial concentration of the biochemical agent.
- k_1,k_2,k_3,k_4 are constants.

3 Non-dimensionalizing the equation

The constants in the equation:

Constant	**Dimension**
s_o	$conc$
k_1	$\frac{1}{time}$
k_2	$\frac{1}{time}$
k_3	$\frac{conc}{time}$
k_4	$conc$

The following substitutions were done:

$$g = xk_4$$

$$t = \tau \frac{k_4}{k_3}$$

This reduces the equation to the final dimensionless form:

$$\frac{dx}{d\tau} = s - rx + \frac{x^2}{1+x^2} \tag{2}$$

where s represents the biochemical signal.

4 In the absence of the biochemical signal

In the absence of the biochemical signal, the Equation(2) reduces to:

$$\frac{dx}{d\tau} = \frac{x^2}{1+x^2} - rx \tag{3}$$

4.1 Analysis

The fixed points of Equation(3) were observed by plotting the two functions

$$y = rx \qquad\qquad y = \frac{x^2}{1+x^2} \tag{4}$$

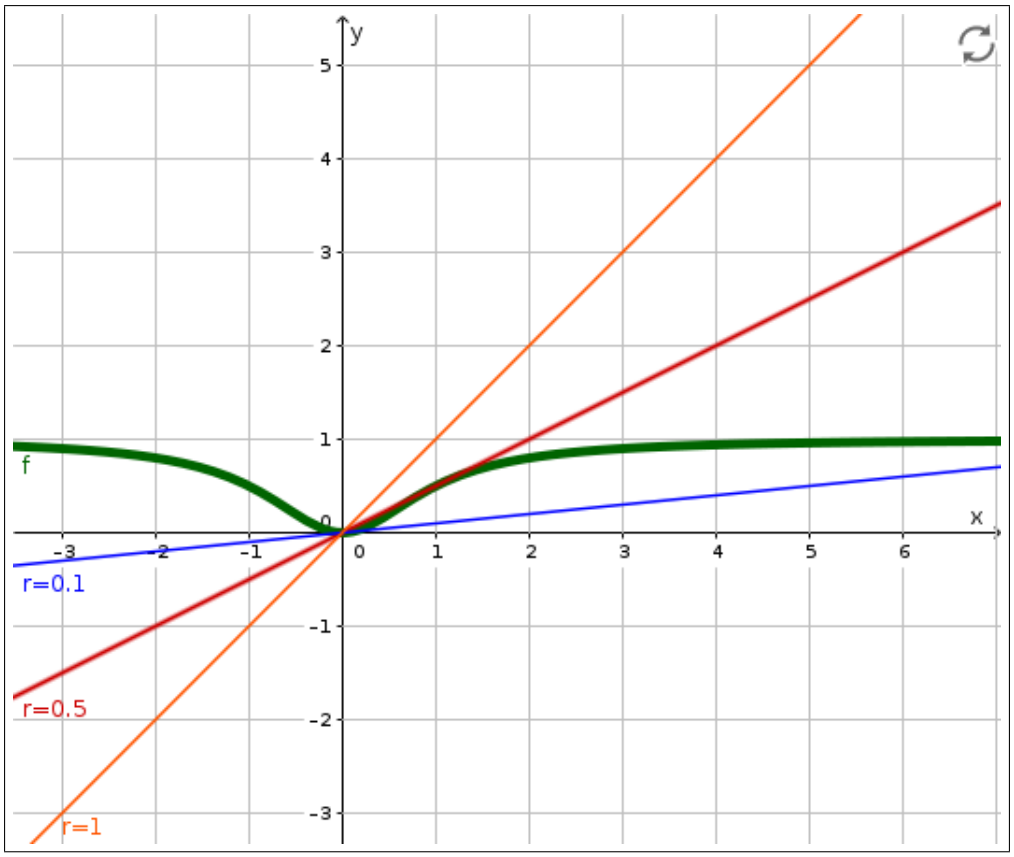

Figure 1: The plot to determine the fixed points for s=0. The bold green line shows the function $\frac{x^2}{1+x^2}$. The others lines represent the curve rx various values of r (0.1, 0.5, 1). The Equation (3) has 3 fixed points for low values of r, then as r increases beyond a threshold r_o, two of the fixed points collide and vanish (saddlenode bifurcaion), and only the fixed point r=0 remains.

4.2 The value of r_o

r_o is calculated by equating the slopes of the above Equations (4), since that is the value of r where the annihilation of the fixed points takes place.
$r_o = 0.5$

4.3 The Bifurcation Plot

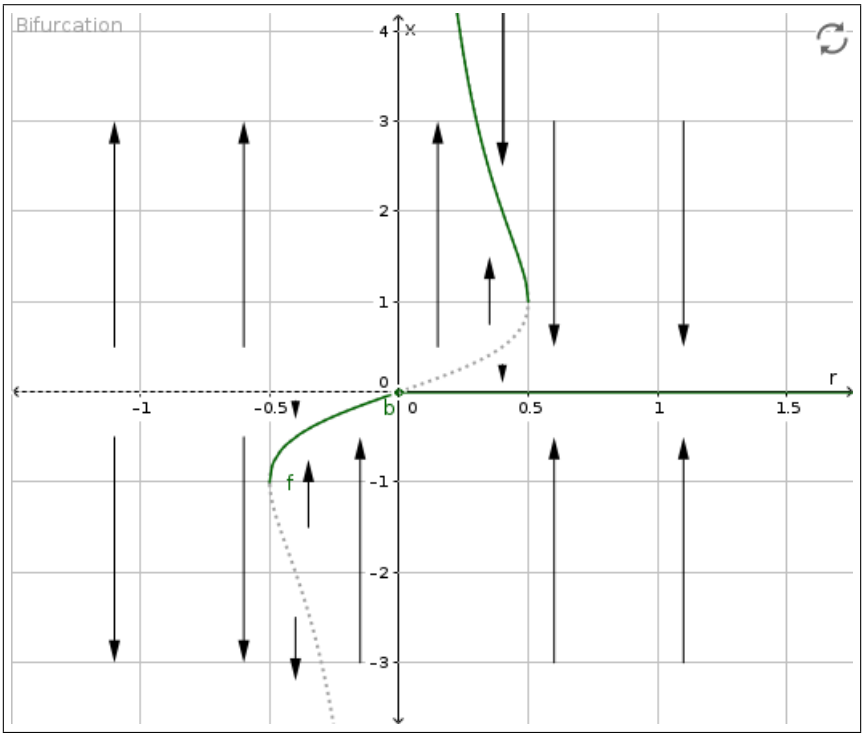

Figure 2: The bifurcation plot for Equation (3). The dashed lines show the unstable fixed pints and the solid lines show the stable fixed points.The arrows indicate the flow. Let us say that the initial concentration of the gene is x_o (non zero). As r is increased from 0, the concentration of x jumps to the upper stable region. This is the part where the feed-forward term dominates and gene is switched on. However, beyond r=r_o(0.5), the negative term starts dominating and bring the value of x towards the lower fixed point, effectively making the concentration of the gene equal to zero.

5 The Biochemical signal

Now we consider the biochemical trigger (Equation (1)). The concentration of the trigger is slowly increased from s=0.

5.1 Analysis

The fixed points of the Equation (1) were observed by plotting the functions:

$$y = s \qquad\qquad y = rx - \frac{x^2}{1+x^2} \tag{5}$$

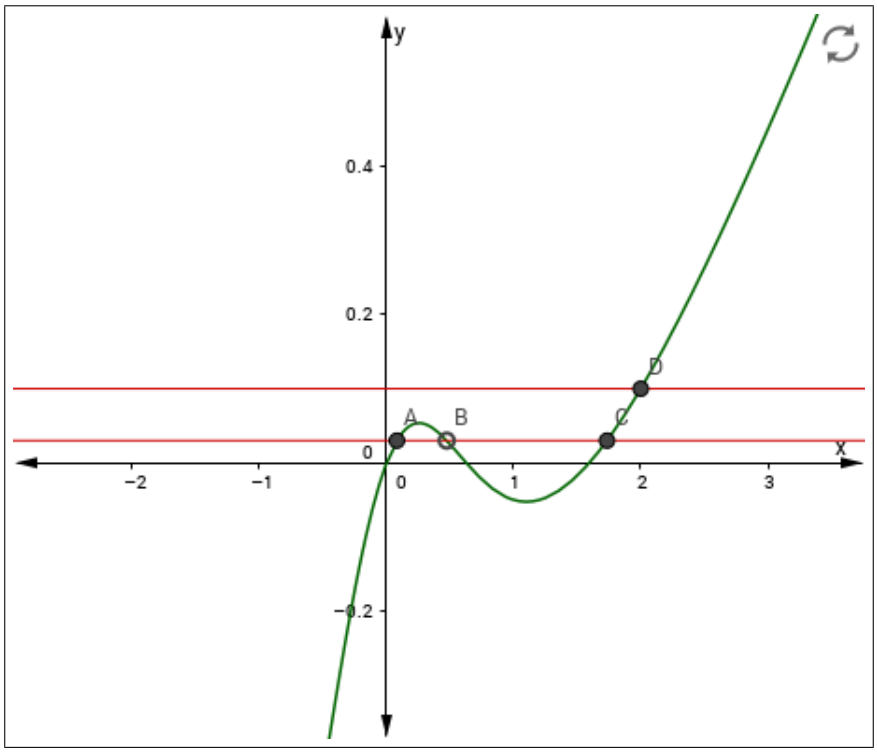

Figure 3: Plot for the fixed points of Equation (1). The green line represents the function $rx - \frac{x^2}{1+x^2}$ and the lines parallel to x-axis represent y=s for different values of s (0.03, 0.1). Putting s=0.03 gives us 3 fixed points (represented in the Fig as A, B, C), with A and C stable, B unstable. Consider the initial concentration of the gene to be 0. As the concentration of s is increases, x chases the fixed point A and the gene is activated. Now consider the situation where the concentration of s goes beyond the local maxima and reaches s=0.1. The fixed points A and B come closer and annihilate, leaving only one, stable fixed point D which now drives the concentration of the gene. This is the **switching on** mode of the biochemical signal. Further, let us now reduce the concentration of s and bring it down to 0 (**switching off**). However, the concentration of x does not go back to 0. Instead, it stays at the stable fixed point D. Thus, the gene, once turned on **cannot be turned off again by the biochemical agent**.

5.2 Varying r

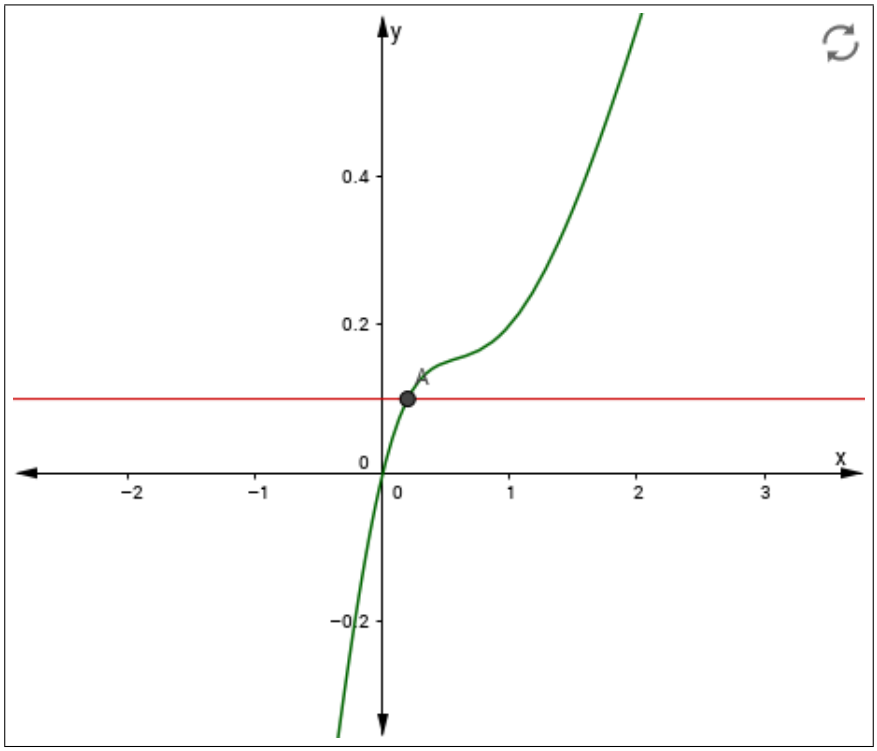

Figure 4: Plot for r=0.7. The green line represents the function $rx - \frac{x^2}{1+x^2}$ and the red line parallel to x-axis represent y=s for s=0.1. With an increase in the value of r, we get only one stable fixed point for any value of s. Therefore, now the gene can be turned off by reducing the concentration of the biochemical trigger and taking it to zero.

6 R-S Plane Visualization

Finally, we attempt to show the variation of the switching phenomena in the r-s plane. For this purpose, we consider Figure 4. At the saddle node point, the values of f(x) and f'(x) are zero. This gives us s and r as functions of the parameter x.

$$r = \frac{2x}{(1+x^2)^2} \qquad\qquad s = \frac{x^2 - x^4}{(1+x^2)^2} \tag{6}$$

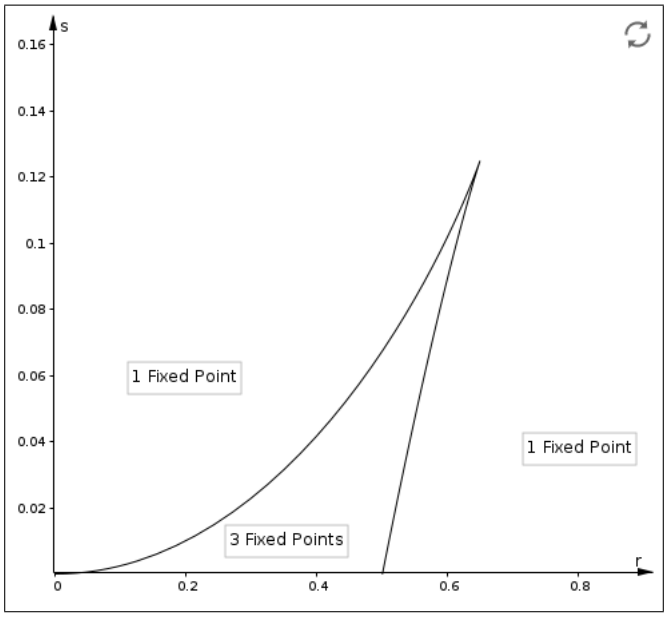

Figure 5: The r vs. s curve. Starting from the origin, as the value of s is increased keeping r small, we get 3 fixed points. Beyond the threshold value of s, two points get annihilated and only one fixed point remains(refer Section 4.1). Further, if we keep s small and increase r, there is only one (stable) fixed point (refer Section 4.2).

6.1 Biological Significance

Biological systems with pattern formation must be small, else the cell has to make use of external signals (switches) to active genes. A key feature of these biological switches is the occurrence of at least two stable states, which can be modeled effectively through a saddlenode bifurcation. Also, once triggered, the activation must be independent of the triggering signal. This is similar to pattern formation, and requires a direct or an indirect autocatalytic activation of genes, as modeled by the equation presented in the report (Equation 1). As an example, the first term in Equation 1 refers to the basal production rate independent of the amount, the second term to linear decay which might be protein decay or dephosphorylation and the third term for example to gene expression via transcription and translation in a genetic switch[2].

References and Bibliography

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[3] Steven Strogatz; Nonlinear Dynamics and Chaos

[4] Lewis et. al (1977)

[5] GeoGebra; International GeoGebra Institute