University of Bristol

Faculty of Engineering

Mathematical Modelling in Physiology and Medicine

Synthetic Gene Network for Entraining and Amplifying Cellular Oscillations

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Abstract

Synthetic biology aims to provide the framework for analysing gene networks by understanding and engineering biological networks that perform a quantitative dynamic function in organisms. In this report, we focus on synthetic oscillatory gene networks. Oscillations are important in a wide range of natural operations such as circadian rhythms, cardiac function, cell division, and hormonal regulation, as well as key to building synthetic control systems that rely on precise timing. Here we model and discuss in silico the phase-plane, nullclines and bifurcations of Hasty's synthetic gene network.

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Introduction

Hasty aims to suggest a model for a robust synthetic oscillator using a pair of ODEs that can retain the ability to function in the presence of environmental perturbations. It uses the topology of two plasmids that have the same promoter; A plasmid with cI gene promoter, when bound to a specific site (OR2) while another site (OR3*) is left vacant, results in an amplified transcription rate of the promoter. While when the second plasmid (lac gene) is bound to the second site (OR3*), the gene is inhibited from transcription (Figure 1). This model is proposed to characterize the dynamics of the Smolen oscillator (Figure 2). The features of which were described by Purcell as "*robust and highly tuneable, able to display periods over a fivefold range, characteristics observed in natural oscillators; robustness provides reliability, while tunability provides utility."* (Oliver Purcell, 2010)

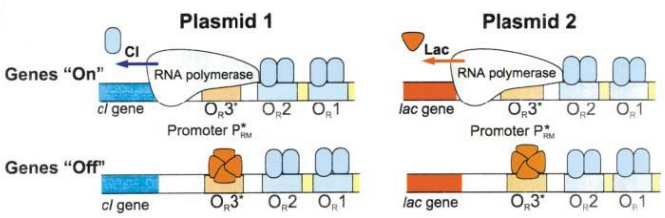

Figure 1:Gene state with binding of dimers to specific sites (Jeff Hasty, 2002)

Figure 2: Suggested topology of a Smolen Oscillator. Gene A is self-activating, whilst also activating gene B. Gene B is self-repressing whilst also repressing gene A

Hasty's model can be presented by analysing the change in concentrations of the two plasmids over a period. The following equations were derived to show the evolution of concentration of the 2 dimers (CI and Lac) over time.

Equation 1

$$\frac{dx}{dt} = \frac{1 + x^2 + \alpha\sigma x^4}{(1 + x^2 + \sigma x^4)(1 + y^4)} - \gamma_x x\,,$$

$$\tau_y \frac{dy}{dt} = \frac{1 + x^2 + \alpha\sigma x^4}{(1 + x^2 + \sigma x^4)(1 + y^4)} - \gamma_y y\,.$$

Concentration change in CI is denoted by *dx/dt* and concentration change in Lac is denoted by *dy/dt*. 'α' represents the increase in transcription rate when cI binds to OR2.'σ' represents the affinity for a CI dimer binding to OR2 relative to binding at OR1(another binding site on the promoter fit for CI dimers), γ_x and γ_y are the degradation rate for plasmids x and y. Whilst τ_y is the time scale variable for y. With these parameters fixed we can model and analyse the Hasty oscillator. Figure 3 and Figure 4 below show the change in concentrations of dimers over time. (fixed parameters $\alpha=11$, $\sigma=2$, $\gamma_x=0.105$, $\gamma_y=0.036\text{-}0.038$)

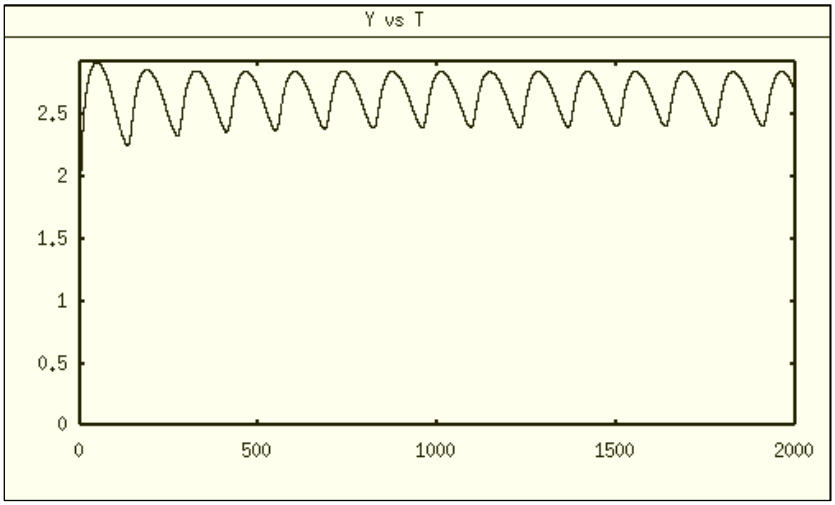

Figure 3: Change in Lac over time

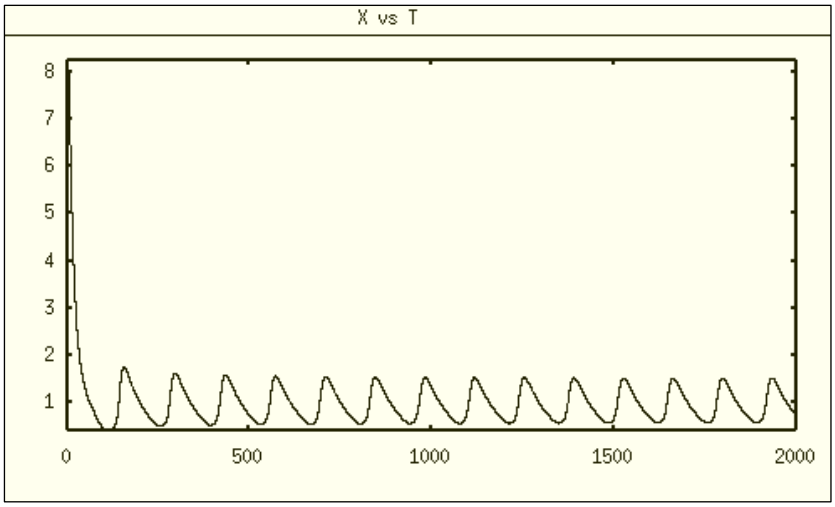

Figure 4: Change in CI over time

Methodology

With the above representation of oscillatory change in concentration in both dimer concentrations, we can now depict the phase plane which would visually display the trajectories of the ODEs, this is shown in Figure 5 below.

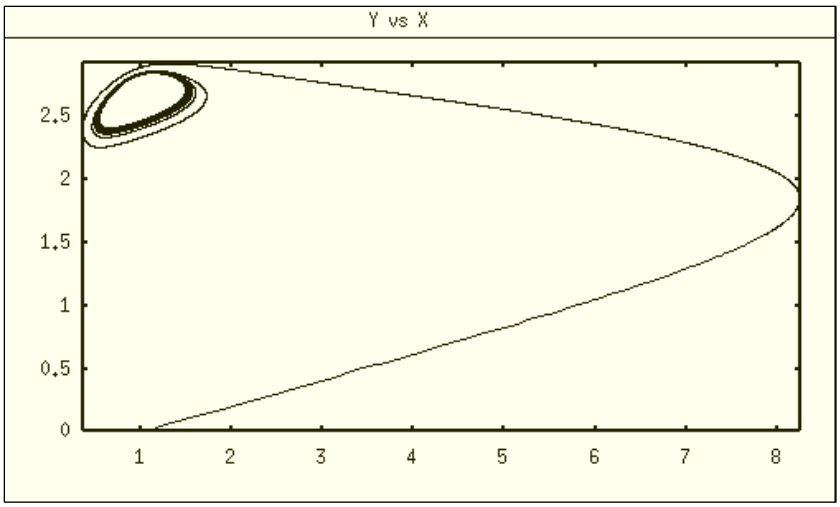

Figure 5: Y vs X Phase Plane diagram

We can also show the nullclines, which are the points where *dx/dt* and *dy/dt* are essentially zero, as we all the direction flow, which represents the solution of the first order differential equation of y(x). Figure 6 depicts both of these.

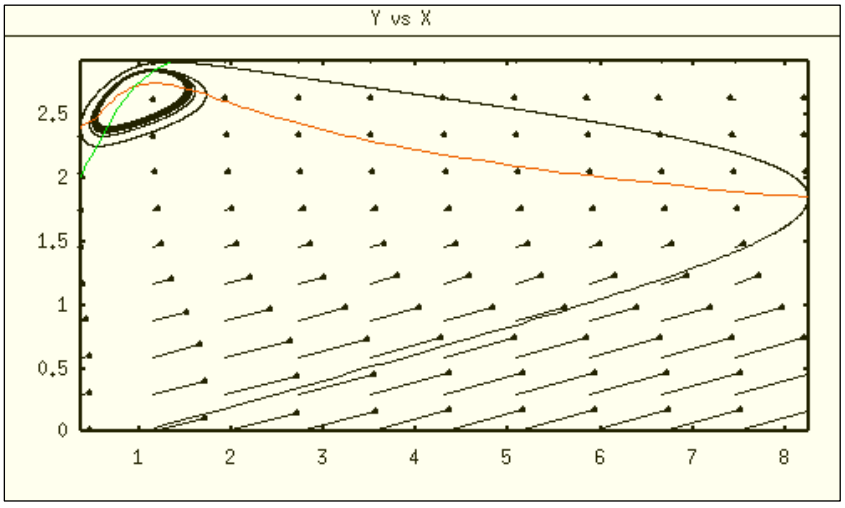

Figure 6: Red and Gren lines represent Nullclines while arrows represent the direct field of y(x)

Analysis

We can now find the bifurcations of the system by analysing the singular points of the system. Singular points or equilibrium points are the points where nullclines intersect, in this system we have only one singular point which is a stable point (Figure 7 below shows the details of the singular point).

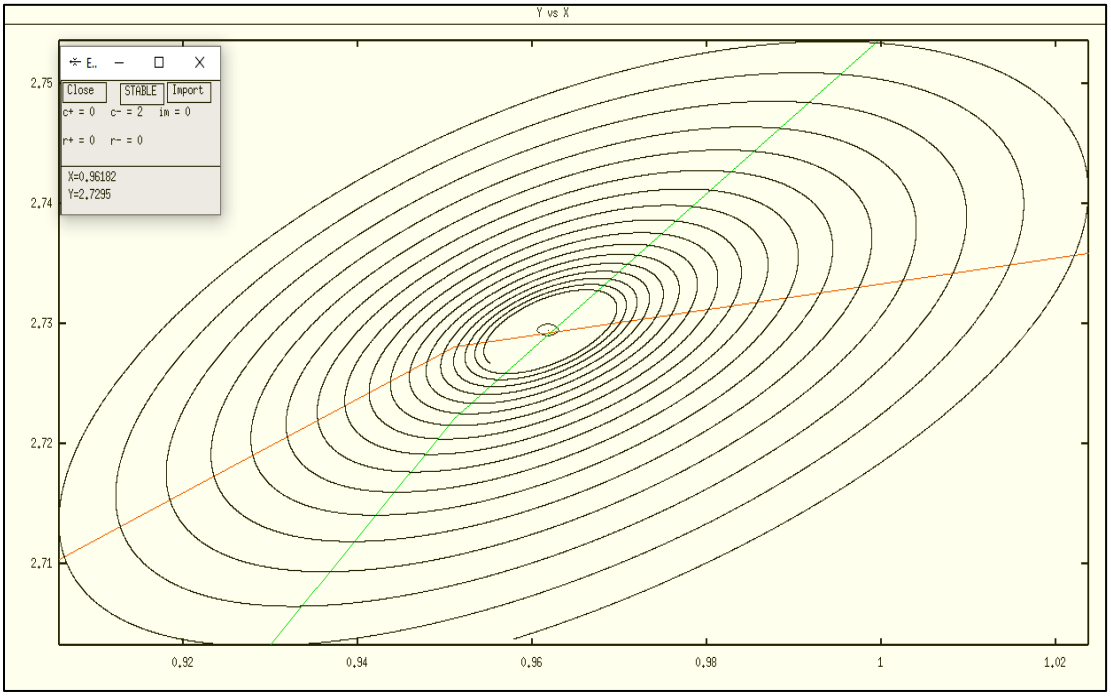

Figure 7: Stable Singular point of system

The convergence of the trajectories of a phase to a focus point shows that the system will switch between a stable and unstable state. This is called a Hopf Bifurcation. Analysing the degradation rates of both dimers, we can see an oscillatory region that grows with increased protein degradation rates (Figure 8) Bifurcation diagrams in terms of γ_x and γ_y both depict the predicted Hopf Bifurcations (Figure 9 and Figure 10). Figure 8 shows that an activator degradation rate (γ_x) two to three times higher than the repressor rate (γ_y) is what causes a Hopf bifurcation. Hence, the supercritical bifurcation in both Figure 9 and Figure 10 depends on the degree of promoter activation for transcription of the activator and repressor genes when dimers bind to a specific site (denoted by parameter α). A narrow region is detected where oscillations and stable equilibrium state coexists. The difference between the two bifurcation is the effects it shows; when γ_y increases, the activator protein X(CI) also increases, while when the rate of degradation of the repressor (γ_x) increases the repressor protein Y(Lac) decreases. This could explain the growth in the oscillatory region with growing degradation rates depicted in Figure 8.

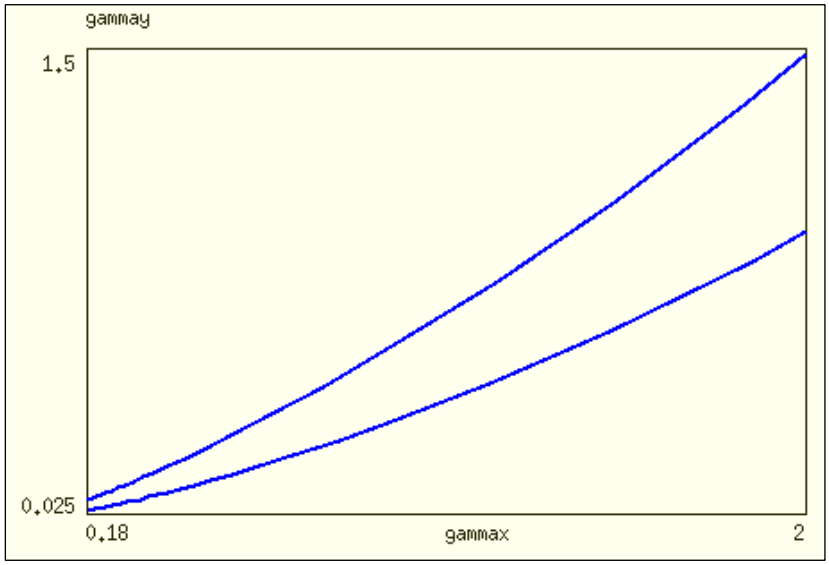

Figure 8: The oscillatory region (between boundaries) grows with increased protein degradation rates.

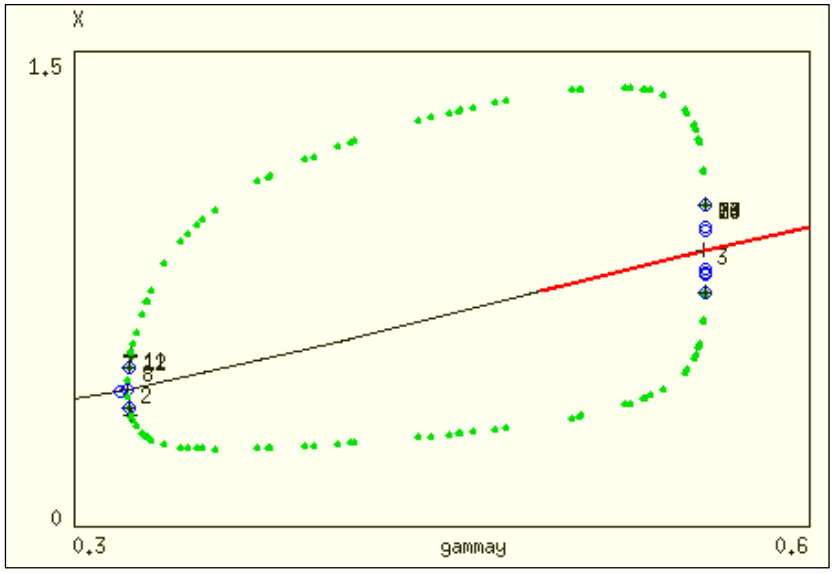

Figure 9: The Hopf bifurcation corresponding to the lower boundary in (a) is supercritical.

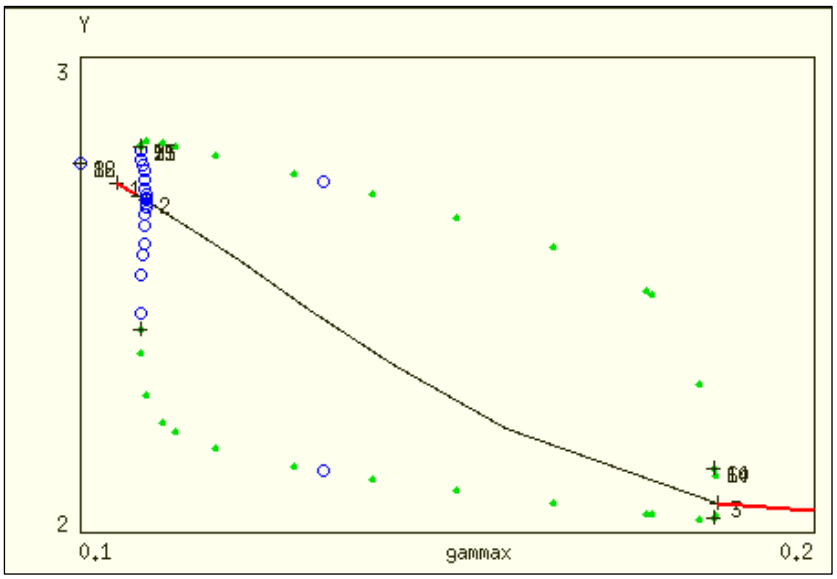

Figure 10: The Hopf bifurcation corresponding to the lower boundary in (a) is supercritical.

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Bibliography

Jeff Hasty, M. D. V. R. a. J. J. C., 2002. Synthetic Gene Network for Entraining and Amplifying Cellular Oscillations.

Oliver Purcell, N. J. S. C. S. G. a. M. d. B., 2010. A comparative analysis of synthetic genetic oscillators.