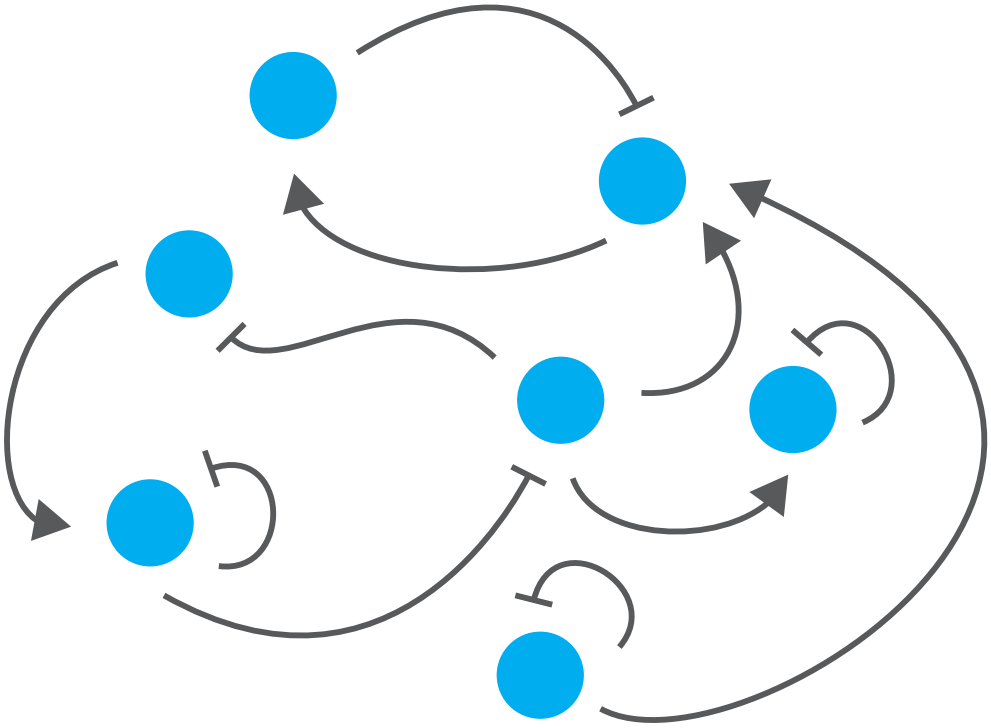
CY Cergy Paris University

Systems Biology
Biological Oscillators



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1 Introduction to Systems Biology

Systems biology is the mathematical modeling of the behavior of complex biological systems using dynamic mathematical models. Biological oscillators are a large part of biology and der are countless examples for the beating of a heart to daily rhythms in human body temperature and hormone secretion In each example, there is a standard oscillation of some period.

Complex biological system can be model by biochemical and genetic networks those diagrams draw the interaction between species in the system with themselves and one another. species involved in the interaction in the networks The abundance of each species is assigned to a state variable within the model.
All these state variables are called the state of the system. it gives a full description of the system's status at any given time. Besides variables of state, models also introduce parameters, whose values are fixed. Model parameters identify environmental effects like degradation, interactions in the networks also can have parameters.

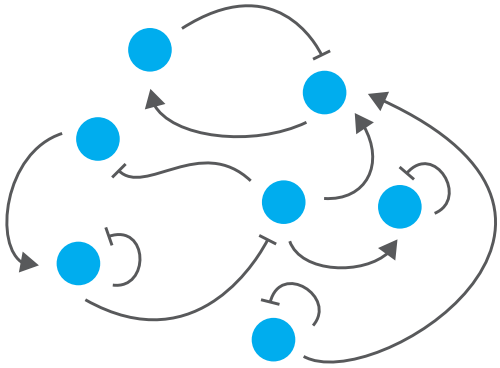

Figure 1: Biological networks.

That can be modeled by a biological network for instance, $X \rightarrow Y$ is a network that controls the production rate of protein Y the activator X and for repressor is described by blunt-headed arrow $X \dashv Y$. where the arrows not only express the activation or the repression of genes it also communicates numbers that correspond to the strength of the interaction. essentially it just the strength activation or the repression of the gene defined by input function [1].

for a biological system, the input function is generally a Hill function to establish those processes,it is derived from the equilibrium binding of the activation factor to the promoter.

There are two types Hill functions of first an increasing function when X is an activator and a decreasing function when X is a repressor .
Hill input function for an activator$f\left(X^{\star}\right)$ is a curve that rises from zero and approaches a maximal saturated level Fig(2).

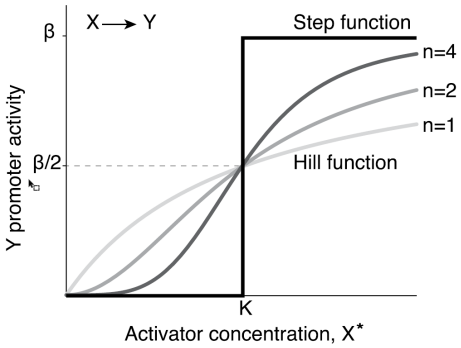

Figure 2: Hill input function for an activator.

$$f\left(X^{\star}\right)=\beta\frac{X^{\star n}}{K^{n}+X^{\star n}} \qquad (1)$$

The Hill function has three parameters, K, β, and n. where K is the activation coefficient, it determines the activation of X for eq1 we can see that half-maximal expression is reached when $X^{\star}=K$. The next one is the maximal

promoter activity, β. Maximal activity is reached at high activator concentrations. The last variable in this function is the hell coefficient n represents the steepness of the input function, the steepest the function is the larger n.

On the other hand, the Hill input function is a decreasing curve Fig(3) , whose shape depends on three similar parameters with the hill function becomes :

$$f\left(X^{\star}\right)=\beta\frac{K^{n}}{K^{n}+X^{*n}} \tag{2}$$

In the model that I am going to present we only need to know that gene expression is the process by which the instruction in our DNA is converted into a functional product in our case that is a protein, that last one can act as activators and represses of genes.

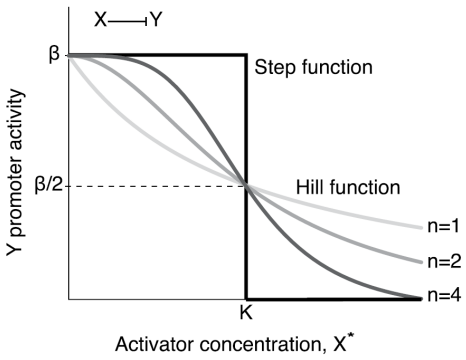

Figure 3: Hill input function for a repressor.

2 How to build a Biological Oscillator

2.1 Negative feedback and Delay

Oscillations require negative feedback and delay let's start with the negative feedback loop a simple "example genes" where gene X decrease its own amounts by producing its own repressor see Fig(4) .
this simple network mathematically can be model in this differential equation :

$$\frac{dX}{dt}=\beta\frac{K^{n}}{K^{n}+X^{n}}-\alpha X \tag{3}$$

and since it is a one-dimensional system and we have $X_{st}>0$ form the Fig(4) and

$$\frac{dX}{dx}<0$$

that gives us a stable point and there is no oscillation to have oscillations we need another piece which is a delay.

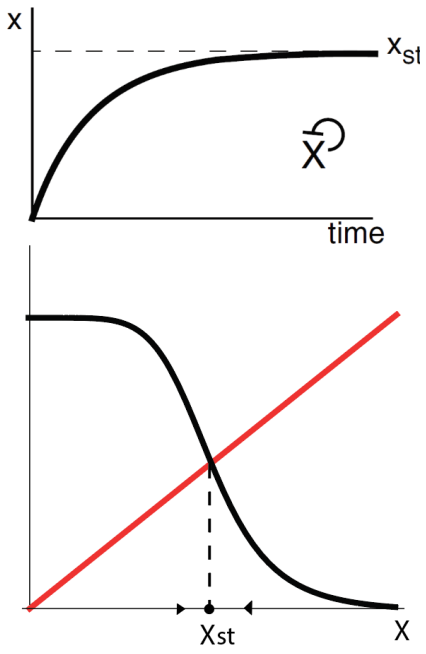

Figure 4: Negative feedback

To produce a delay into the biological network we to add an element to our negative feedback loop we can do that by another gene species G_2. such that G_1 activates G_2 according to the increasing Hill function $g(G_1)$ and G_2 represses G_1 according to the decreasing Hill function $f(G_2)$

$$\begin{aligned} \frac{dG_1}{dt} &= f\left(G_2\right) - \alpha_1 G_1 \\ \frac{dG_2}{dt} &= g\left(G_1\right) - \alpha_2 G_2 \end{aligned} \tag{4}$$

Where there α_1 and α_2 are the degradation rate for each gene species.
now to study the dynamics of the system we need to compute that Jacobian matrix at the fix-point :

$$J = \begin{bmatrix} \frac{\partial \phi}{\partial x} & \frac{\partial \phi}{\partial y} \\ \frac{\partial \psi}{\partial x} & \frac{\partial \psi}{\partial y} \end{bmatrix} \tag{5}$$

where $\phi(x, y) = \frac{df(G_1)}{dt}$ and $\psi(x, y) = \frac{df(G_2)}{dt}$ the dynamic of the system can be determined from the two eigenvalues λ_1 and λ_2.

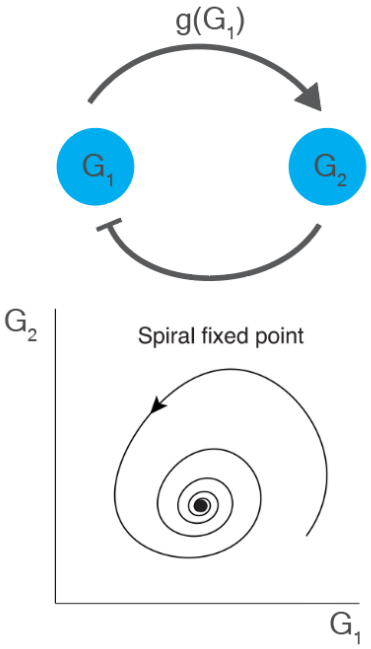

Figure 5: Network diagram for feedback loop with the delay and spiral fixed point.

Moreover, if we set up our system correctly so that $\frac{\partial \phi}{\partial x} > 0$ and $\frac{\partial \phi}{\partial y} < 0$ by ϕ setting as a hill descending function we will get so one of the eigenvalues is imaginary and that gives us damped oscillations because of the degradation of each gene.
We can set up a small script in python to simulate this network code is in the appendix :

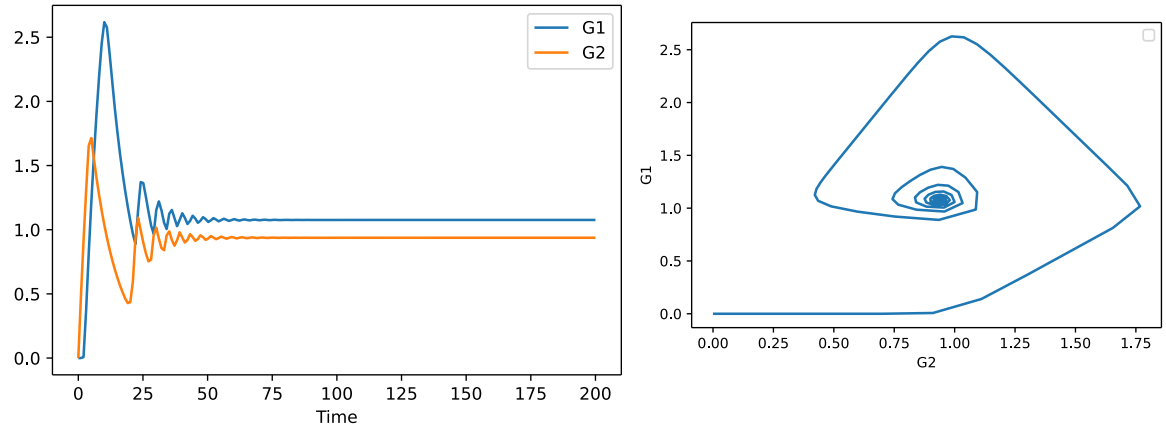

Figure 6: Damped oscillations

we can see that we got the corresponding result from the theory, a damped oscillation and spiral fixed point.

2.2 A Toy model of Biological Oscillators

One of the earliest examples of mathematical modeling dates back to 1999 by Brian C. Goodwin [2] began modeling for biological oscillators, the oscillator is based on a negative feedback loop comprising a chain of three variables, X, Y, and Z, where Z inhibits the production of X.

In the last section, we achieved oscillations but it was damped oscillations since the genes get degrade over time because the rate of degradation is analogous to friction in physics.

In our last model, We are going to use a similar approach to Goodwin oscillator to a model of genes oscillation. As last time G1 activates G2 according to the increasing Hill function G2 activates G3 likewise but for G3 act as represses for G1 (negative feedback loop).

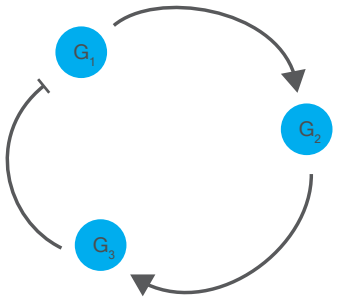

Figure 7: Network diagram for feedback loop with the delay

$$\begin{aligned}
\frac{dG_1}{dt} &= \frac{1}{1+G_3^n}\beta_1 - \alpha_1 G_1 \\
\frac{dG_2}{dt} &= \frac{G_1^n}{1+G_1^n}\beta_2 - \alpha_2 C_2 \qquad (6) \\
\frac{dG_3}{dt} &= \frac{G_2^n}{1+G_2^n}\beta_3 - \alpha_3 G_3
\end{aligned}$$

And that gives us a system of a differential equation and they can be implemented using Python

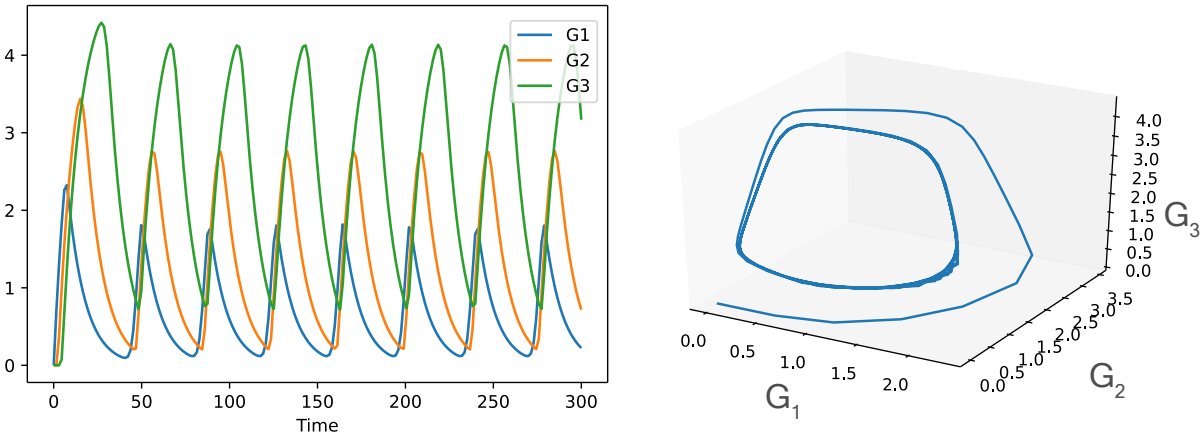

Figure 8: Oscillations using three Genes

By solving equations numerically obtain oscillation of the three genes in the Fig(4) we can see that is a limit cycle in 3D where trajectory approaches the limit cycle, and it is a stable limit cycle it's a common thing in a biological system.

3 Conclusion

In conclusion modeling biological oscillator allow me to understand what how to set biological network and how for this network we generate a mathematical model to understand the dynamics using a system of partial differential equations with it input functions to model those systems.

References

[1] Uri Alon. "An Introduction to Systems Biology: Design Principles of Biological Circuits (2ed ed.)" In: (2019).

[2] Brian C. Goodwin. "Oscillatory behavior in enzymatic control processes". In: *Advances in Enzyme Regulation* 3 (1965), pp. 425–437. ISSN: 0065-2571. DOI: https://doi.org/10.1016/0065-2571(65)90067-1. URL: http://www.sciencedirect.com/science/article/pii/0065257165900671.