Modelling Biochemical Oscillators

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1 Protein Regulation Overview

The production of various proteins from the original DNA sequence is one of the most important biological processes to happen in organisms. However, it is important that the rate at which various proteins are produced is regulated and remains at homeostasis, as an imbalance could potentially lead to various other negative implications. This regulation is important because differing amounts of proteins can affect the rate and by how much other processes occur within a particular organism.

The overall process of protein production form the original gene sequence can be broken down into transcription and translation. In transcription, the base sequence from the DNA is encoded into a strand of messenger RNA (mRNA). In translation, the mRNA is then converted into a sequence of proteins that is determined by the base sequence. The rate at which both transcription and translation occurs can be physically quantified by the concentrations of both mRNA and protein that are present. This can be quantified by the law of mass action, which states that the rate at which a reaction occurs is proportional to the product of the concentrations of the reactants. By using this mechanism, along with the connection between the different molecules involved, this allows the process to be regulated by creating both a negative and a positive feedback loop.

The process begins with the production of mRNA due to the transcription from DNA. The mRNA is then translated into the sequence of protein, hence increasing the concentration of protein. The protein is autocatalytic, which in essence means that it is able to upregulate its translation rate upon an increase in concentration. However, whilst an increase in protein concentration increases translation rate, it downregulates transcription rate. This continues until s time at which there is a large amount of protein, but the transcription rate is very low such that the amount of mRNA becomes comparatively small. This is due to the natural degradation of mRNA.
Due to the decreased concentration in mRNA, the rate of translation now decreases. This continues until a time at which the translation rate of mRNA to protein is superseded by the natural degradation, at which point the overall concentration starts to now decrease.
Since the amount of protein has now decreased, this also means that there is less inhibition of the transcription process, which means that the production of mRNA can finally start to increase again. The concentrations of both mRNA and protein and the transcription and translation is now at a similar level to that at the beginning of the process, and thus completed one full oscillatory cycle. The entire process now repeats, and thus produces the oscillatory behavior as observed. A diagram depicting the whole process is shown in Figure 1:

Note that in this process one can identify two feedback loops, one positive and one negative. The positive feedback loop can be identified in the autocatalytic translation of the mRNA into the protein, which is catalysed by the protein itself. The negative feedback loop can be identified in the downregulation of transcription due to inhibition caused by the protein product. These two feedback mechanisms combine together to create the characteristic oscillatory behaviour.

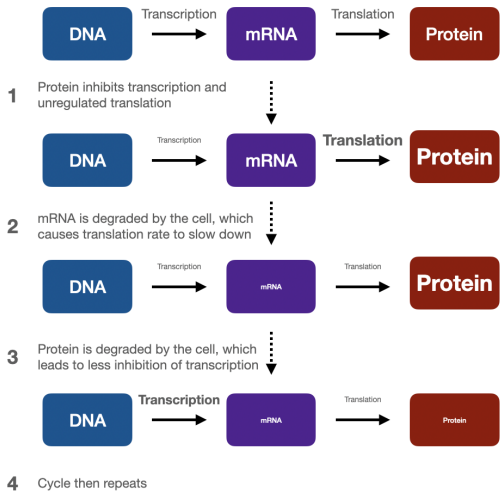


Figure 1: Diagram showing the protein regulation model described by Caicedo-Casso et al [1], in which there is a negative feedback loop in which the protein product inhibits its own transcription combined with its autocatalytic translation. In this diagram, a larger text corresponds to an increased amount of that quantity.

2 Model Simulation

2.1 Protein Regulation Model

The process of protein regulation can be represented by a simple model characterised by a set of parameters. By considering the various chemical reactions which occur in this process, the concentrations of mRNA and protein (M and P) can be related to the various processes which determine their respective production and degradation rates. The wiring diagram showing this process is given in Figure 2. From the law of mass action, these chemical reactions can be formed

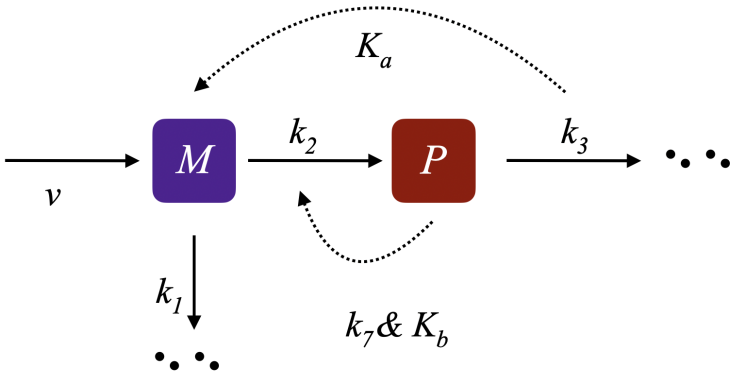


Figure 2: Wiring diagram describing the the model above in terms of the various reaction parameters that control the rates of transcription and translation. All units of concentration are arbitrary (a.u). v is the synthesis rate which is given in a.u per hour. k_2 characterises the translation rate from mRNA to protein, and also has units of a.u per h. k_1 and k_3 characterize the degradation of mRNA and protein respectively, and have units of per h. K_a and K_b are related to the critical concentration values for inhibition and activation respectively, and have arbitrary units. m and n are dimensionless Hill coefficients that represent cooperativity of kinetics.

into two coupled differential equations that relate the concentrations of mRNA and protein to the

rates of both transcription and translation:

$$\frac{dM}{dt} = -k_1 M(t) + \frac{\nu}{1 + (P(t)/K_a)^m} \tag{1}$$

$$\frac{dP}{dt} = k_2 M(t) + \frac{k_7 M(t) P(t)^n}{K_b^n + P(t)^n} - k_3 P(t) \tag{2}$$

The above two equations can then be solved numerically using a differential equation solving algorithm, the code for which is given at the bottom of this report.

2.2 Solutions

2.2.1 Characteristic Oscillatory Behaviour

To solve these two equations numerically, the solver "ode45" [2] will be used. This particular solver implements a Runge-Kutta method with a variable time step that optimises computation speed. A plot of the solutions for the mRNA and protein concentrations ($M(t)$ and $P(t)$ respectively) is given in Figure 3. From Figure 3, a characteristic oscillatory motion is observed in the majority

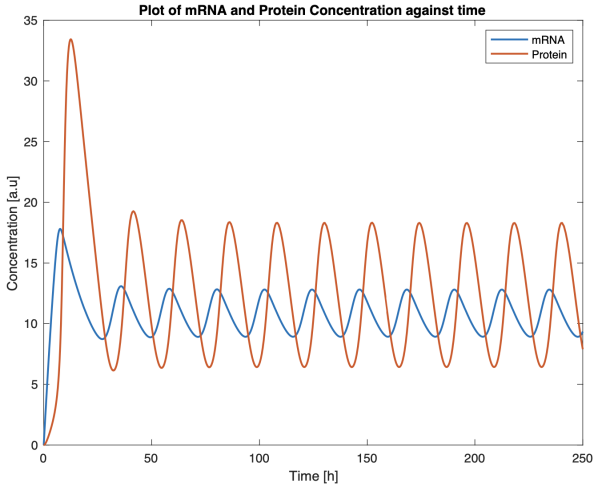
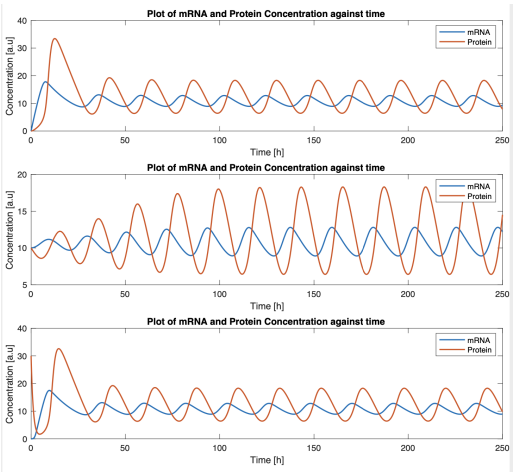


Figure 3: Solutions to Equations (1) and (2) in the domain $0 < t < 250$h. The initial conditions were such that both concentrations were zero at the start (At $t = 0$, $M(t) = P(t) = 0$) In this simulation, the following parameters used were those given in Caicedo-Casso et al. [1] $\nu = 3.26$, $k_1 = 0.045$, $k_2 = 0.161$, $k_3 = 0.869$, $k_7 = 2.174$, $K_a = 5.5$, $K_b = 15$, $m = 3$, $n = 2$.

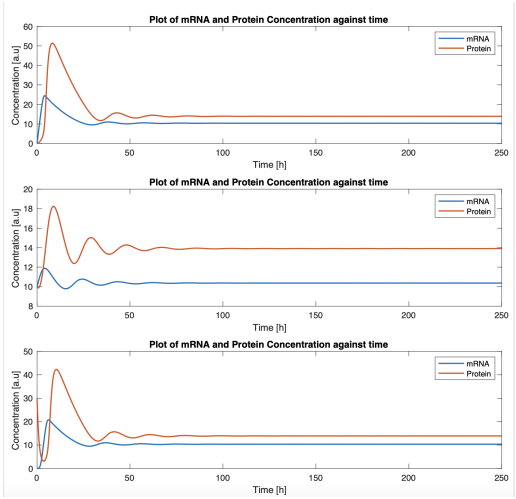
of the time domain in both the mRNA and protein concentration, as predicted by the model. The two cycles have the same periodicity which is due to the fact that they are both intimately linked. The peak in mRNA concentration occurs slightly before that of the protein, which makes biological sense due to the presence of mRNA eventually leading to the production of protein via the process of translation.
During the first couple of oscillations, there is a notable deviation, with the protein concentration in particular rising to a large level. This is due to the fact that the system has a temporary period of instability as it has yet to settle down to a regular rhythm. It then changes towards a more regulative behaviour within just a couple of cycles.

2.2.2 Parameter Variation

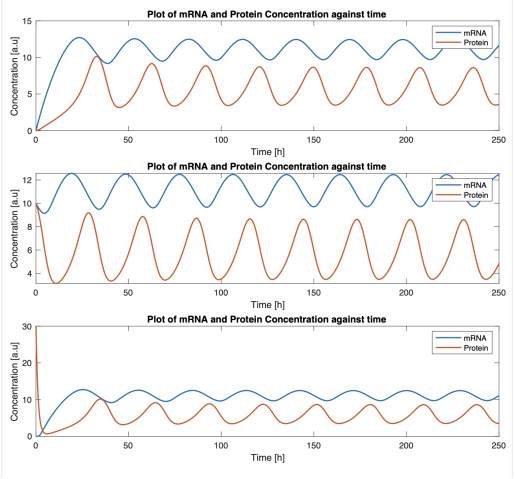
The system is able to show somewhat different behaviour given a change in the initial conditions and the parameters. In particular, this paper will be investigating how a change in the parameter ν (which characterises the mRNA synthesis rate) affects the system along with varying initial conditions. These simulations are shown in Figure 4.



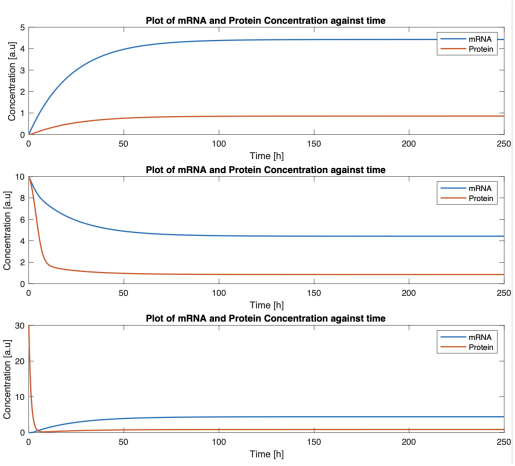
(a) Simulation of the model with $\nu = 3.26$ with varying initial conditions: Top: $P(0) = M(0) = 0$, Middle: $P(0) = M(0) = 10$, Bottom: $P(0) = 30, M(0) = 0$



(b) Simulation of the model with $\nu = 8$ with varying initial conditions: Top: $P(0) = M(0) = 0$, Middle: $P(0) = M(0) = 10$, Bottom: $P(0) = 30, M(0) = 0$



(c) Simulation of the model with $\nu = 1$ with varying initial conditions: Top: $P(0) = M(0) = 0$, Middle: $P(0) = M(0) = 10$, Bottom: $P(0) = 30, M(0) = 0$



(d) Simulation of the model with $\nu = 0.2$ with varying initial conditions: Top: $P(0) = M(0) = 0$, Middle: $P(0) = M(0) = 10$, Bottom: $P(0) = 30, M(0) = 0$

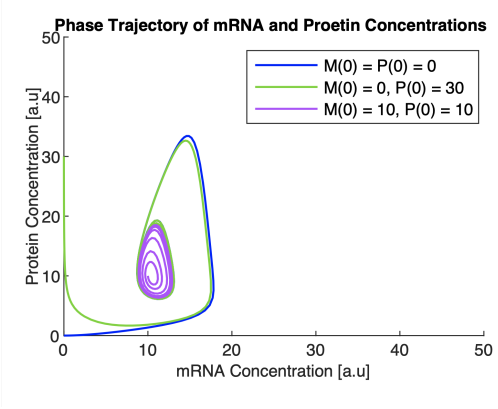
Figure 4: Set of solutions to Equations (1) and (2) in the domain $0 < t < 250$h. In these runs, three different initial conditions were used along with four different values of the parameter ν.

From Figure 4 is is clear that the value of the parameter ν has a large effect on the time evolution of the system. In some cases (Figure 4a and Figure 4c), oscillatory behaviour is observed throughout the entirety of the time duration, with both $M(t)$ and $P(t)$ each fluctuating between two concentrations. However, if the value of ν becomes too large (Figure 4b), the oscillations become highly suppressed very quickly and both $M(t)$ and $P(t)$ each settle to a single constant value. This corresponds to lack of change in the rates of both transcription and translation keeping the concentrations of mRNA and protein very constant and highly regulated at two very distinct values. By contrast, if the value of ν is less than 1, the type of behaviour observed changes entirely, as seen in Figure 4d. Instead, no oscillatory behaviour is observed at all and both $M(t)$ and $P(t)$ concentrations gradually settle towards a constant concentration, which causes little to no change in the transcription and translation rates and hence no further change in the concentration.

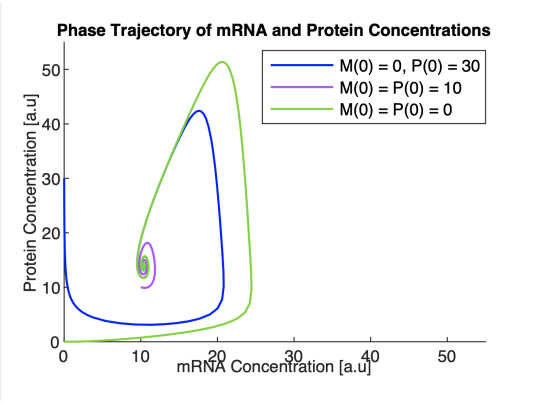
3 Bifurcation Analysis

3.1 Dynamics in the Phase Plane

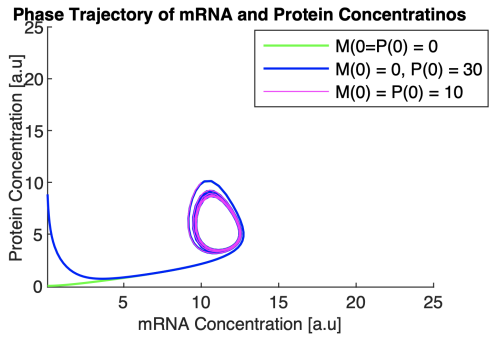
The same model of protein regulation can be represented in the phase plane, with the two axes being mRNA and protein concentration ($M(t)$ and $P(t)$). In this representation, the shape of the trajectories of both the mRNA and protein concentrations will yield the nature of their time evolution. The solutions in time either converge to a single, unchanging value (steady state) or oscillate indefinitely between two values. In the phase plane representation, trajectories that converge to a single value will have a single end point while trajectories that oscillate indefinitely will exhibit elliptical type motion. As before, the parameter ν will be varied to investigate how trajectories in the phase plane differ for different values. All simulations in the phase plane were performed using the numerical bifurcation package MatCont [3]. Figure 5 shows these trajectory simulations with the same values for of ν along with the same three initial conditions.



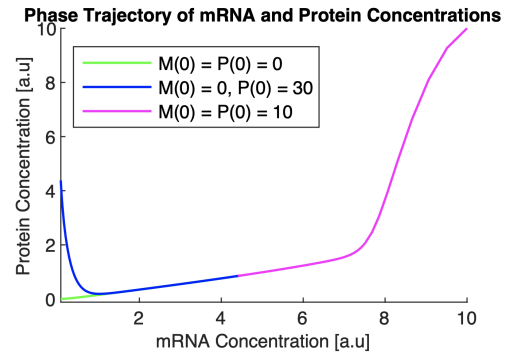
(a) Phase trajectory of the model with $\nu = 3.26$ with varying initial conditions: Blue: $P(0) = M(0) = 0$, Pink: $P(0) = M(0) = 10$, Green: $P(0) = 30, M(0) = 0$.



(b) Phase trajectory of the model with $\nu = 8$ with varying initial conditions: Green: $P(0) = M(0) = 0$, Pink: $P(0) = M(0) = 10$, Blue: $P(0) = 30, M(0) = 0$.



(c) Phase trajectory of the model with $\nu = 1$ with varying initial conditions: Green: $P(0) = M(0) = 0$, Pink: $P(0) = M(0) = 10$, Blue: $P(0) = 30, M(0) = 0$.



(d) Phase trajectory of the model with $\nu = 0.2$ with varying initial conditions: Green: $P(0) = M(0) = 0$, Pink: $P(0) = M(0) = 10$, Blue: $P(0) = 30, M(0) = 0$.

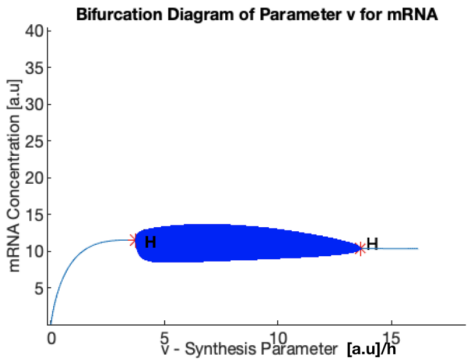
Figure 5: Set of Phase trajectories with mRNA concentration $M(t)$ along the abscissa axis and protein concentration along the ordinate axis. In these runs, three different initial conditions were used along with four different values of the parameter ν.

In accordance with Figure 4, Figure 5 shows that it is clear that changing ν will affect the trajectory of the curve in the phase plane. In all runs in Figure 5, varying the initial conditions had no effect on the final position in the plane. While the trajectories for different initial conditions clearly differ for a given ν, the outcome of whether the trajectory converges to a single point or traces out an ellipse was the same across different initial conditions. Inspecting each simulation individually, the final trajectories in Figure 5a and Figure 5c were both elliptical, whereas for

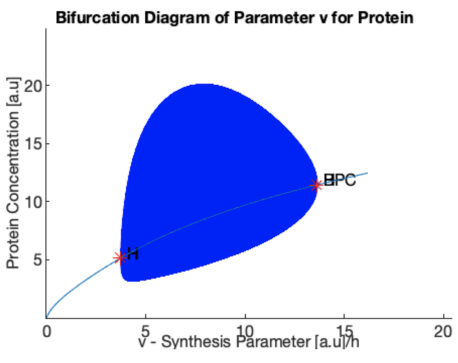
Figure 5b and Figure 5d the trajectories converged to a single point in the phase plane. This is in accordance with Figure 4.

3.2 Bifurcation Analysis

The dependence of the behaviour of the system on the synthesis rate ν can be illustrated using a bifurcation diagram, with ν being the bifurcation parameter. From Figure 5, the system can exhibit either oscillatory or stationary behaviour which are dependent on the parameter ν. This indicates that for certain values (Hopf points) of ν, the stability of system suddenly changes. A bifurcation diagram of the parameter ν for both the mRNA and Protein concentration solutions is shown in Figure 6. These two types of behaviours shown can explain the difference in qualitative behaviours



(a) Bifurcation diagram for mRNA concentration $M(t)$, with all other parameters as before.



(b) Bifurcation diagram for Protein concentration $P(t)$, with all other parameters as before.

Figure 6: Bifurcation diagrams showing the tipping points between stable and unstable equilibrium solutions for both mRNA and Protein concentrations, with Hopf points marked as H. In both cases, Hopf bifurcation occurs at $\nu = 3.77$ and $\nu = 13.69$. Between these values, oscillatory behaviour is observed, fluctuating between the highest and lowest points in the blue region (eigenvalues for a particular value of ν).

in Figure 4. One can also notice that the thickness of the blue region decreases for higher values of ν. This behaviour results from the autocatalytic nature of the protein production. As ν increases, an increase in the mRNA results in reaching the maximum value for autocatalytic behaviour faster which then leads to a decreased production of mRNA synthesis resulting in decrease of the overall period in which this process happens.
One can also note that there is a difference between the mRNA and Protein diagrams. Figure 6a shows a sharp rise for small values of ν, but then reaches a turning point, after which the mRNA concentration is largely unaffected by increasing ν. This happens before the first Hopf point. By contrast, Figure 6b shows a much more steady increase in the Protein concentration, and still increases in the blue region, before showing a gradual decrease for larger values of ν. This can be explained by the fact that ν has a much more direct influence on the mRNA than the protein since by definition it is the transcription parameter.

4 Summary

In conclusion, this model of Protein synthesis regulation proposed by Caicedo-Casso et al [1] is able to predict the correct behaviour of the two feedback mechanisms. Using certain range of values of the mRNA synthesis parameter, an oscillatory behaviour is shown in both mRNA and Protein concentrations with a slight phase difference. This is what one would expect in a real biological system. Using values outside this range lead to somewhat different behaviour, with both mRNA and protein concentrations remaining steady. In all simulations, the initial conditions were found to have no difference to the long term outcome of the system as the system would always reach this stable state after only a few cycles. Bifurcation analysis has showed that there are certain

values of the transcription parameter for which the behaviour of the system changes from being stationary to oscillatory. The corresponding Hopf points were shown to be the same for both mRNA and Protein, and the period was shown to decrease for increased transcription rates, an expected behaviour shown in many biological systems. As in any biological system, a simple model is unable to provide a full description of how the system works, as there are a very large number of factors to consider which is difficult to take into account. This is by no means the full description of Protein regulation as in reality neither the oscillatory Period nor the Parameters used be fixed, rather they would be influenced by other processes. Overall this model is able to successfully describe many aspects of the nature of protein regulation, and could be readily extended to many other oscillatory biological processes.

References

[1] Caicedo-Casso A, Kang H. W , Lim S, Hong C. I Robustness and period sensitivity analysis of minimal models for biochemical oscillators. Sci Rep. 2015 Aug 12;5:13161. doi: 10.1038/srep13161. Erratum in: Sci Rep. 2016;6:18504. PMID: 26267886; PMCID: PMC4542697. [Accessed 20 Jan 2021]

[2] Nur Adila Faruk Senan, "A brief introduction to using ode45 in MATLAB" http://www.eng.auburn.edu/~tplacek/courses/3600/ode45berkley.pdf [Accessed 24 Jan 2021].

[3] Hil Meijer, "Matcont Tutorial:ODE GUI version" https://wwwhome.ewi.utwente.nl/~meijerhge/MT_instructions.pdf [Accessed 26 Jan 2021].