Computational Systems Biology

Stochastic dynamics of regulated expression

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1 Introduction

Gene regulation is the process by which cells control the expression of their genes, resulting in the production of different proteins and ultimately, different cell behaviors. This regulation is essential for proper cellular function and differentiation, and is achieved through the interaction of various regulatory molecules, such as transcription factors.

Deterministic dynamics and stochastic dynamics are two different mathematical approaches used to model gene regulation. Deterministic dynamics assumes that the behavior of the system is entirely predictable, based on a set of deterministic equations that describe the interactions between different components. In the context of gene regulation, these equations describe the rates of transcription (synthesis of RNA from a DNA template where the code in the DNA is converted into a complementary RNA code) and translation (synthesis of a protein from an mRNA template where the code in the mRNA is converted into an amino acid sequence in a protein).

Stochastic dynamics, on the other hand, takes into account the inherent randomness and variability of biological systems. Rather than assuming a single outcome for each interaction, stochastic models use probability distributions to describe the likelihood of different outcomes. One common method for simulating stochastic dynamics in gene regulation is the Gillespie algorithm, which can be used to simulate the constitutive expression of a gene, where mRNA is transcribed from DNA and then translated into protein. The algorithm works by simulating the occurrence of individual reaction events, such as transcription and translation, using random numbers to determine the time until the next event and which event occurs.

In this assignment, three different cases for gene regulation are studied, each one of them through a deterministic dynamics simulation and a stochastic dynamics simulation. In the first part, a default case is studied, where the initial concentrations of both mRNA and proteins are 0. In each simulation there are four parameters that define the gene regulation, which are: α_m (mRNA synthesis), δ_m (mRNA degradation), α_p (protein synthesis) and δ_p (protein degradation). In the second case, the original parameters are modified in order to make the transcription rate higher than the default case, but the translation rate is smaller. Finally, in the last case, the effect of negative feedback is studied, where instead of having a constitutive expression of the genes (the expression occurs continuously and at a constant level), there is a regulated expression (the expression is controlled by specific signals and varies in response to changes in the environment or cellular state). In this specific case, a negative feedback means that the expression of genes is downregulated in response to the product it produces, resulting in a decrease in the overall level of product.

To carry out this assignment, two different programs have been made using Python language: one for the deterministic dynamics and another one for the stochastic dynamics (Gillespie algorithm).

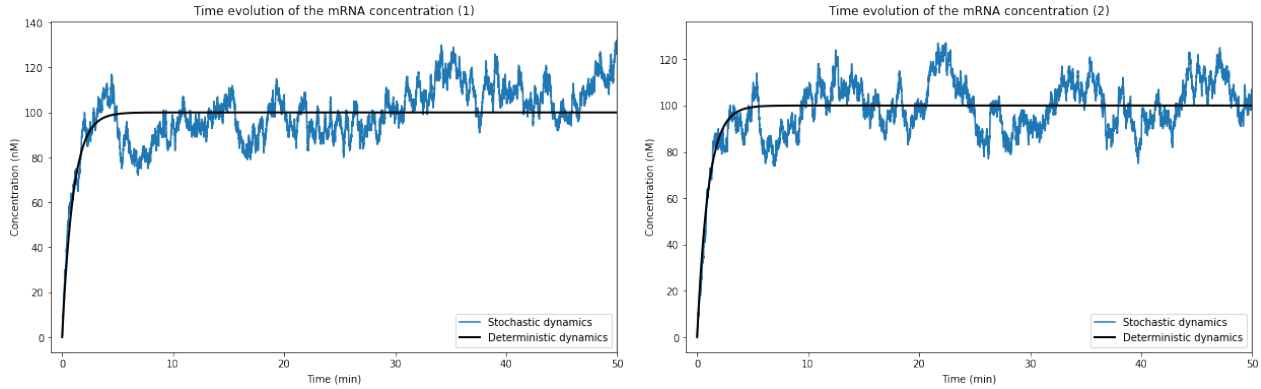
2 Results

2.1 Constitutive expression: default case

We start by using the following parameter values: $\alpha_m = 100nMmin^{-1}$, $\delta_m = 1min^{-1}$, $\alpha_p = 10min^{-1}$, $\delta_p = 0.1min^{-1}$. The initial conditions must be all concentrations zero: $[protein]_{t=0} = 0$, $[mRNA]_{t=0} = 0$. For the stochastic dynamics, a volume of $V = 1\mu m^3$ must be used. The deterministic and the stochastic dynamics are simulated until the steady state is reached, for a total of 100 realizations (figures 1, 2 and 3). We expect to see a growth of both the protein and the mRNA concentrations, until both of them become stable.

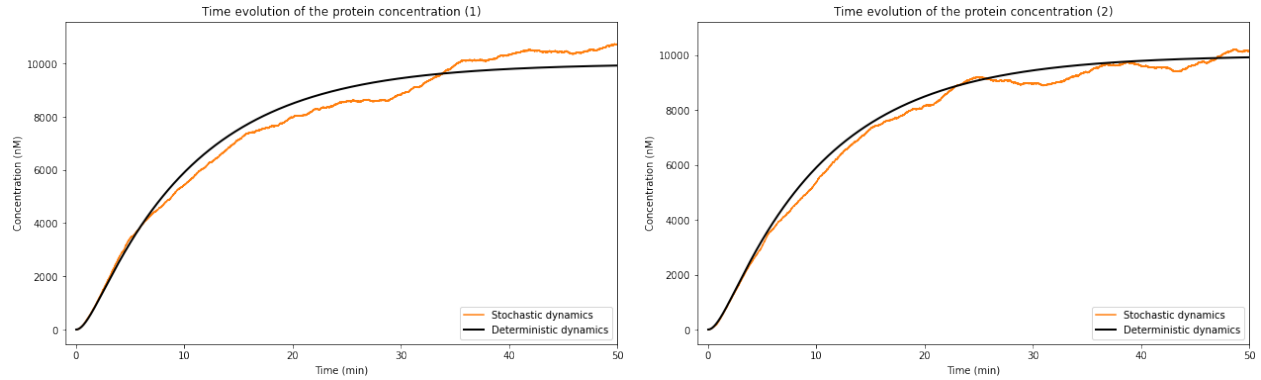
A second simulation carried out only with the stochastic dynamics program must be made in order to plot concentration histograms for the mRNA and protein concentrations (figures 4 and 5). For this simulation, the initial conditions correspond to the deterministic stationary values, and it is simulated for a total of 1000 realizations.

- Figure 1: time evolution of the mRNA concentration, for the deterministic dynamics and for two realizations of the stochastic dynamics.



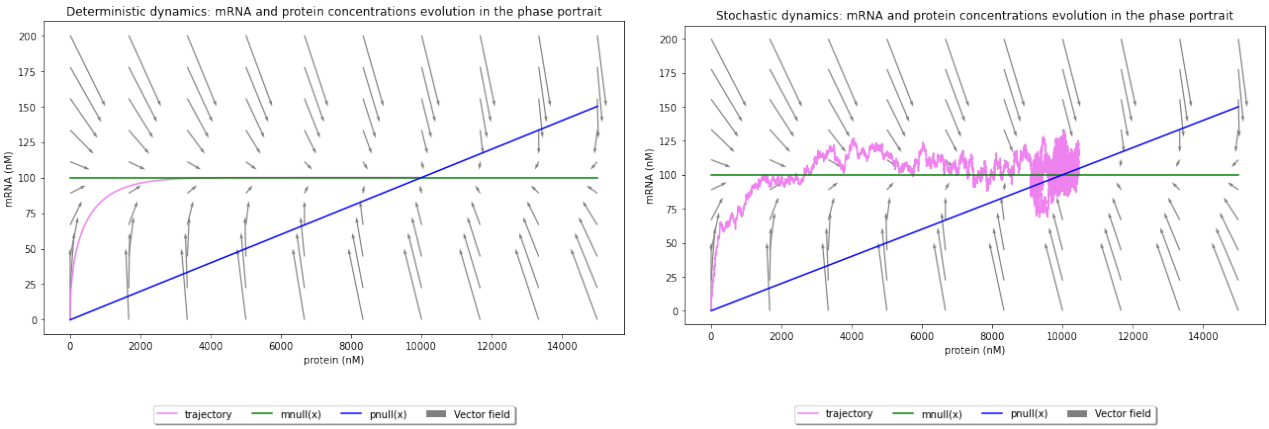
We can see that the mRNA concentration increases with time, becoming stable after around 5 minutes, and reaches a final concentration of 100 nM. It is clear that the stochastic dynamics simulation follows a similar pattern as the deterministic dynamics simulation.

- Figure 2: like Figure 1 but for the protein concentration.



The protein concentration also increases over time, but more slowly than the mRNA concentration. This happens because a minimum concentration of mRNA is required in order to start the protein synthesis, and the translation process is slower than transcription. The steady state is reached after around 50 minutes, having a final protein concentration of 10,000 nM. We can also see how the stochastic dynamics simulation has the same curve shape as the deterministic dynamics simulation.

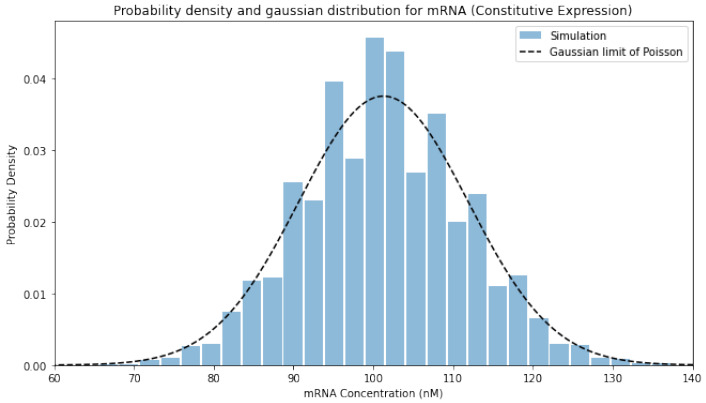
- Figure 3: mRNA and protein concentrations evolution (for the deterministic dynamics and for 1 realization of the stochastic one) in the phase portrait, depicting the nullclines and vector field.



The vector field points to the most stable state of the system, which corresponds to a mRNA concentration of 100 nM, and a protein concentration of 10,000 nM. In the stochastic dynamics simulation, we can see how the points of the *trajectory* curve pile up around the steady state point.

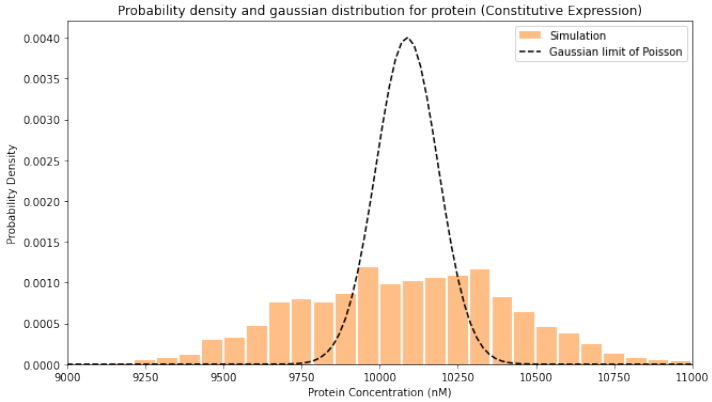
In all these simulations, it is evident that the stochastic results match with the deterministic results, so we can conclude that the simulations are correct. However, we can observe how the deterministic results are more linear than the stochastic ones, since stochastic dynamics simulations are based on random numbers to form probability distributions, and therefore the results obtained have more randomness inside of the lineal behaviour.

- Figure 4: Probability density obtained from the stochastic dynamics simulation for the mRNA concentration. The Gaussian distribution is also plotted, with standard deviation equal to the square root of the mean. As value for the mean, the deterministic stationary value is taken ($100nM$)



We can see how both the histogram and the Gaussian distribution have a peak at 100 nM. This means that the most probable concentration of mRNA in the steady state is 100 nM.

- Figure 5: Like Figure 4 but for the protein concentration. The corresponding Gaussian is also plotted. As value for the mean, the deterministic stationary value is taken ($9925.13nM$)



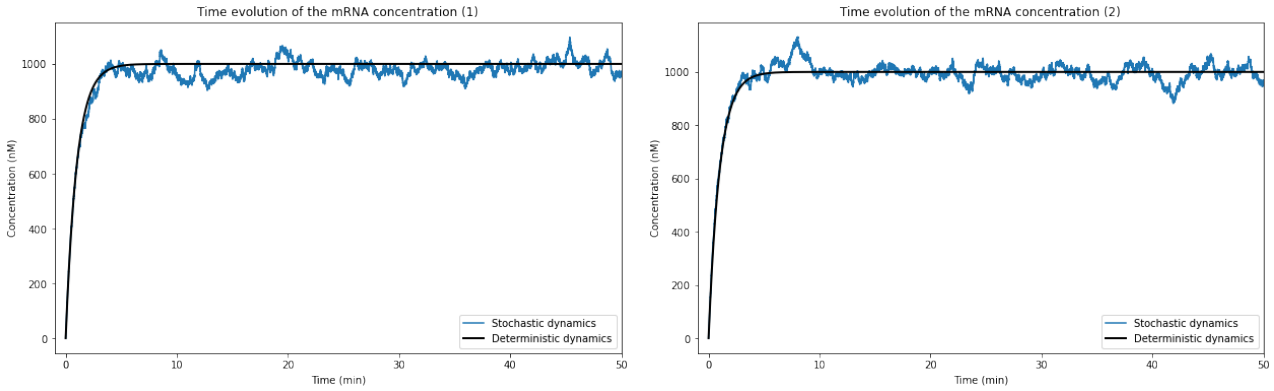
The Gaussian function has its peak at around 10,000 nM. However, this function doesn't exactly fit the numerical data of distribution function, because the bins of the histogram are very scattered.

2.2 Constitutive expression: effect of transcription and translation rates

In this case we want the transcription rate to be 10 times higher than the default case, but the translation rate has to be 10 times smaller. The following parameter values are used: $\alpha_m = 100 \cdot 10nMmin^{-1}$, $\delta_m = 1min^{-1}$, $\alpha_p = 10/10min^{-1}$, $\delta_p = 0.1min^{-1}$. Once again, we start with initial conditions being all concentrations zero, and the simulations for both the deterministic and stochastic dynamics are carried out for a total of 100 realizations until the steady state is reached (figures 6 and 7). Afterwards, a second simulation is carried out through Gillespie algorithm, using a volume of $V = 1\mu m^3$, a total of 1000 realizations and initial conditions corresponding to the deterministic stationary values to plot the histograms and Gaussian functions (figures 8 and 9).

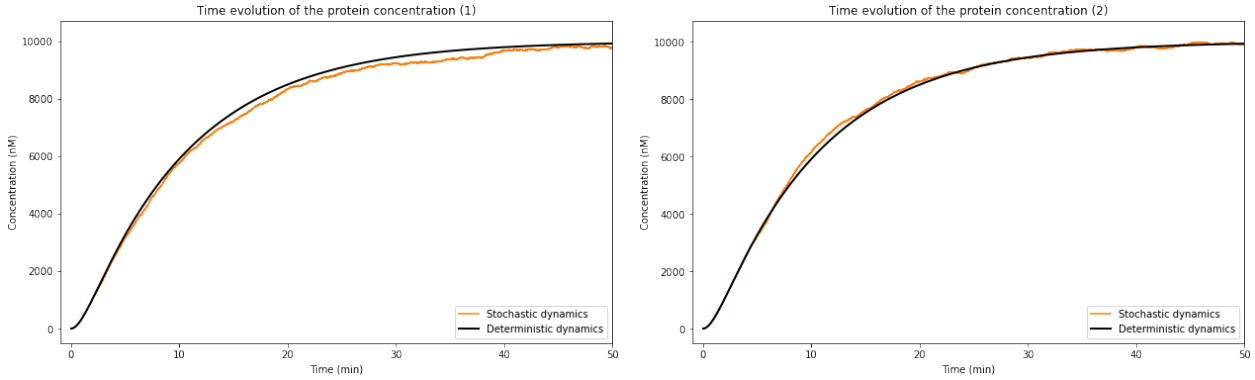
In the scenario shown in the previous chapter (default case), the transcription rate of 100 nM/min generates new mRNA molecules at a faster rate than the mRNA molecules are being consumed by translation and degradation. However, the slower translation rate leads to a slower consumption of mRNA molecules, allowing the mRNA pool to accumulate and reach a steady-state concentration of 100 nM. However, in this case, the transcription rate of 1000 nM/min generates new mRNA molecules at a much faster rate than in the first scenario, but the slower translation rate leads to a slower consumption of mRNA molecules. As a result, the mRNA pool accumulates more rapidly than in the first scenario, so we should expect a higher steady-state concentration of mRNA.

- Figure 6: time evolution of the mRNA concentration, for the deterministic dynamics and for two realizations of the stochastic dynamics.



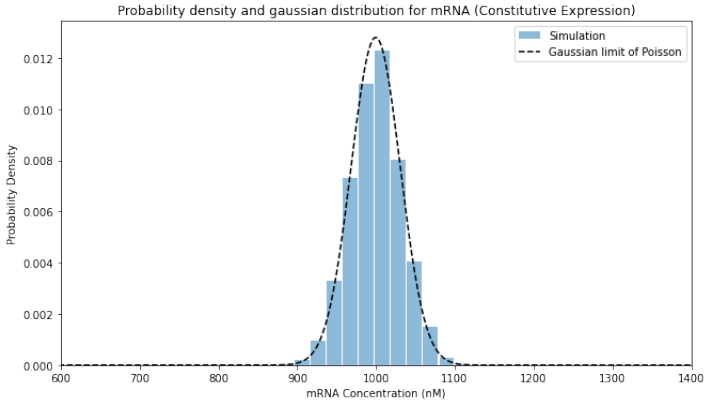
Just as hypothesised, the mRNA concentration increases over time, but this time it reaching a concentration of 1000 nM in the steady state, which is 10 times higher than before. It is also clear how the stochastic dynamics simulation matches the deterministic dynamics simulation.

- Figure 7: like Figure 6 but for the protein concentration.



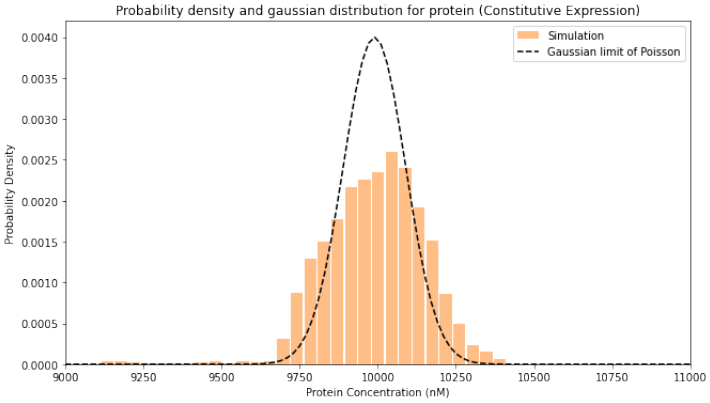
We can see how the protein concentration has not changed, compared to the case seen previously. In this case, the faster transcription rate of 1000 nM/min generates more mRNA molecules that are translated into proteins at a slower rate of 1 min^{-1}. However, the increased supply of mRNA molecules ensures that the rate of protein synthesis remains sufficient to maintain a steady-state protein concentration of 10,000 nM. Therefore, the steady-state protein concentration remains constant.

- Figure 8: Probability density obtained from the stochastic simulations for the mRNA concentration. The Gaussian distribution with standard deviation equal to the square root of the mean is also plotted. As value for the mean, the deterministic stationary value is taken ($1000nM$).



The Gaussian function matches the stochastic results, having a peak at 1000 nM.

- Figure 9: Like Figure 8 but for the protein concentration. The corresponding Gaussian is also plotted. As value for the mean, the deterministic stationary value is taken ($9925.13nM$).



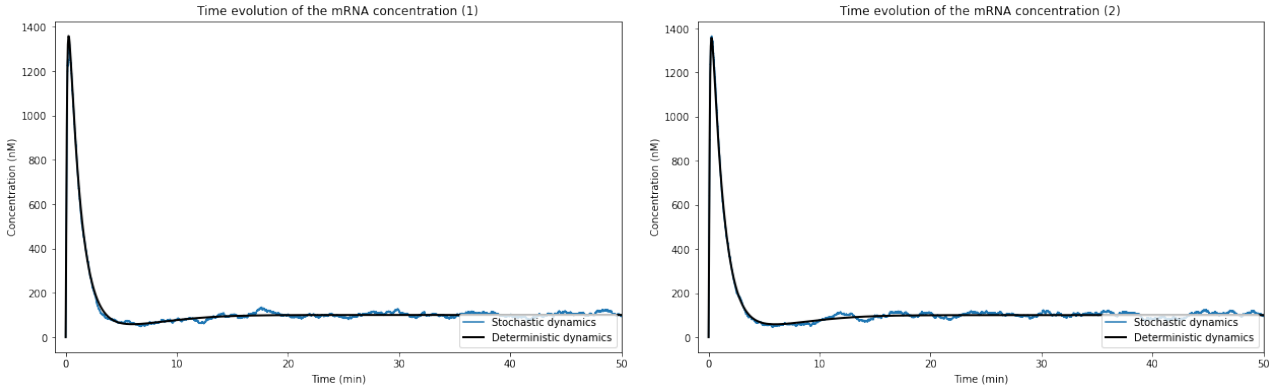
The Gaussian function also matches the stochastic results, even though it does not fit perfectly, since the bins representing the probability densities are a little dispersed.

2.3 Regulated expression: effect of negative feedback

For the last case, a regulated expression through negative feedback is simulated. The parameter values used are: $\alpha_m = 10100 \cdot f_-(P) nM min^{-1}$, $\delta_m = 1 min^{-1}$, $\alpha_p = 10 min^{-1}$, $\delta_p = 0.1 min^{-1}$. The deterministic dynamics is simulated for $f_-(P) = \frac{k^2}{k^2+p^2}$ with $k = 1000nM$ and p is the protein concentration (nM). The stochastic dynamics is also simulated through the Gillespie algorith, for a volume $V = 1\mu m^3$ and $f_-(P) = \frac{k^2}{k^2+p^2}$ with $k = 602$ molecules and P is the number of proteins. This function $f_-(P)$ is the equivalent one of the deterministic dynamics. Once again, we start with initial conditions all zero concentrations (figures 10 and 11). Just like before, we run a second simulation only with the Gillespie algorithm to plot the probability density and the Gaussian distributions for mRNA and protein (figures 12 and 13).

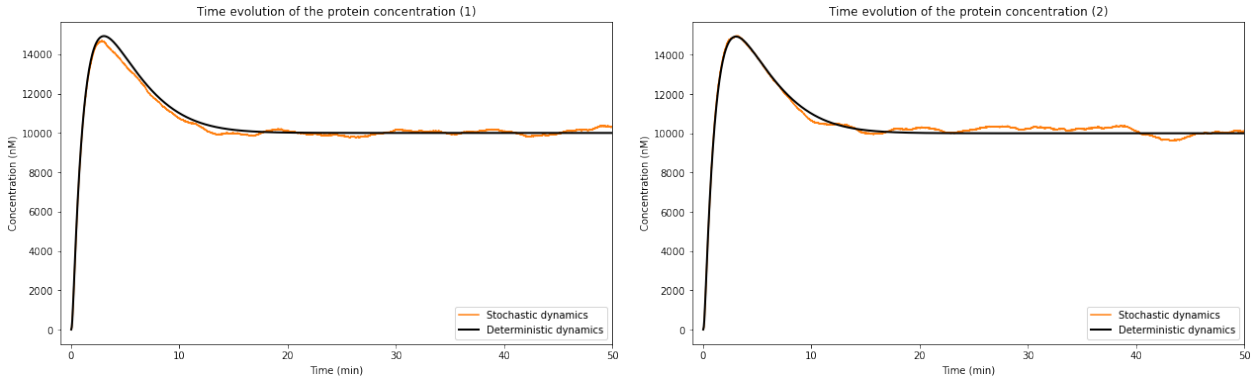
Negative feedback is a regulatory mechanism in gene expression where the product of a gene inhibits its own production. In this mechanism, the expression of a gene leads to the production of a protein that can bind to the promoter region of the same gene and inhibit its own transcription. The main effect of negative feedback in regulated gene expression is to create a stable and precise response to a given stimulus. When a stimulus triggers the expression of a gene, the resulting protein levels increase. However, when the protein levels reach a certain threshold, negative feedback inhibits further gene expression, leading to a decrease in protein levels. This negative feedback loop helps to maintain a stable protein concentration and prevent overexpression or underexpression of the gene. It also enables the system to respond quickly to changes in the environment or stimulus, as the feedback loop can rapidly adjust the expression of the gene to maintain a stable protein concentration.

- Figure 10: time evolution of the mRNA concentration, for the deterministic dynamics and for two realizations (i.e. each a different seed) of the stochastic dynamics.



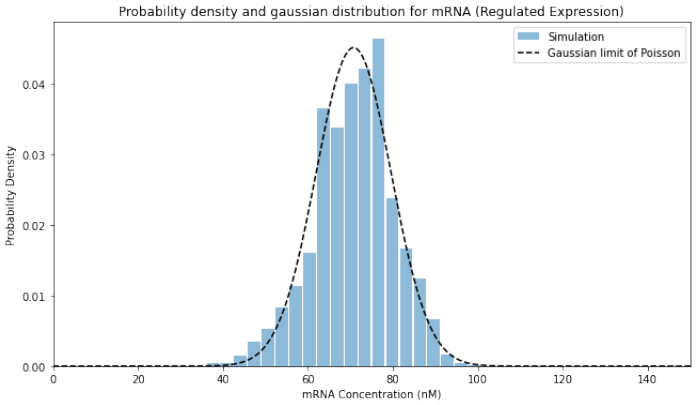
As we predicted, the mRNA concentration raises quickly, but once it reach a concentration around 1300 nM, it starts decreasing rapidly, until it stabilizes at around 110 nM. Again, we can see that for both simulations, the stochastic results match the deterministic results, so we can conclude that the outcome of the simulations is correct.

- Figure 11: like Figure 10 but for the protein concentration.



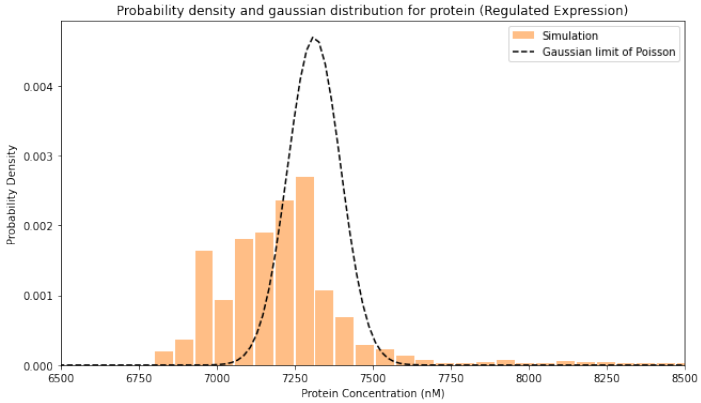
Again, the results obtained match with the results we expected. The protein concentration increases until it reaches a peak of 15,000 nM, and subsequently decreases until it reaches the steady-state, at 10,000 nM.

- Figure 12: Probability density obtained from the stochastic simulations for the mRNA concentration. The Gaussian distribution is also plotted with standard deviation equal to the square root of the mean. As value for the mean, the deterministic stationary value is taken ($100nM$).



For this simulation, a different value of k is used, and therefore the steady-state concentrations differ from the ones shown previously. For the mRNA, the final concentration is 70.76 nM, which matched the peak of the Gaussian function represented. The stochastic results also correlate with the function.

- Figure 13: Like Figure 12 but for the protein concentration. The Gaussian distribution is also plotted with standard deviation equal to the square root of the mean. As value for the mean, the deterministic stationary value is taken ($10,000nM$).



For the protein, we obtain a steady-state concentration of 7312.08 nM. In this plot we can see how the peak of the Gaussian function doen't match the probability density, since the bins are very dispersed (the highest protein concentration obtained before the steady-state is much higher).

3 Conclusions

We can conclude that both the deterministic dynamics and the stochastic dynamics perform very accurate simulations regarding the regulation of genes, either in the constitutive expression and the regulated expression cases. The results obtained in this assignment match with the theoretical hypothesis, so we can conclude that the figures obtained are accurate.