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Influence of Rate Constant on TF Regulated Gene Expression and Effect of Noise

Enakshi Guru

Abstract

Simple mathematical model of gene expression had been studied thoroughly in this paper. It was assumed that protein synthesis and protein decay were deterministic in nature whereas transition from active to inactive state was totally stochastic. The probability distribution function of TF regulated gene was calculated and evidence of binary and graded response had been observed for different reaction rates. Slow and fast kinetics had been studied explicitly for diierent values of rate constants. Different rate constants played a significant role in calculating distribution function (PDF) and mean value of protein expression in TF regulated gene expression. A small change in the value of the rate constant gave a significant change in average protein value. It was seen that rate constants control the variance as well. The randomness of gene expression was reduced with increasing value of one of the rate constants.

Keywords

Transcription factor regulation; Binary and graded response; Rate of protein activation ; Fast and Slow kinetics; Probability distribution function

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1. Introduction

Effect of Gene regulation in expression of gene are studied in details in cell dynamics [1, 2]. When activator or repressor known as transcription factor (TF) binds at the promoter region in one site or in multiple sites, they regulates the gene expression [3,4]. Cellular inducing signal activates the TFs which then bind to appropriate enhancer sequence of DNA. The response to an inducing signal is measured by the amount of protein synthesized by cell in gene expression. The response is found to be either graded or binary [5,6] depending on the relative stability of the activated and deactivated gene.

In a population of similar cells with identical genetic structure having same environmental condition are expected to give similar gene expression. But in reality two distinct subpopulations of genetically identical cells are observed. In one of the subpopulations, the protein level is low whereas in the other subpopulation the protein level is high. A fraction of cells in which the proteins levels are intermediate are designated as low state. These low and high states are gives Binary gene expression [7,8]. It is also been known as the 'all-or-none' phenomenon. Novick and Weiner [7] gave the evidence of this binary of gene expression. Binary gene expression is purely stochastic in nature. TF regulates the gene expression by increasing the concentration of activator or repressor which consequently give rise to the raising of the fraction of cells in the high or low subpopulation.

In Graded response the output i.e. protein concentration varies continuously as the amount of input stimulus varies, until the steady state is achieved. Graded and binary response both can occur in the same system if the rate constants vary accordingly [9].

Gene expression is associated with a chain of biochemical events which are stochastic in nature [10, 11, 12].In our previous paper we have studied thoroughly the stochastic process in E.Coli in case of toggle switch model [13] Binding or unbinding of activator or repressor at promoter region of DNA and binding or unbinding of regulatory molecules in the operator region are probabilistic process. Probabilistic nature behaves as deterministic process when the participant molecules are large in number [14]. Proteins that expressed in a cell exhibit fluctuations around a mean value as a function of time. In a population of similar cells, the protein levels in individual cells at a specific instant of time are not identical but spread around a mean value. Expression of gene also depends on the specific values of rate constant significantly. Thus rate of reaction plays a significant role in gene expression [9] which we have studied in detail.. As the value of rate of reaction increases randomness increases, system requires more time to reach in equilibrium. For very low value of reaction rate the system becomes almost deterministic in nature. Mean value of protein, around which the protein level fluctuates, also changes with the rate constant. For higher value of rate constant mean value is logically in high state. Fluctuation around the mean position give rise noise [15,16,17,18], which is measured extensively in this paper.

This paper is organized as follows. In first part (3.1) we describe a simple model of gene expression combining deterministic and stochastic approach. In this section we assume that gene can switches from inactive to active state randomly but protein synthesis and protein decay are deterministic process. Then we calculate the probability distribution function of stochastically expressed gene. We study the binary and graded respose of gene expression for the same system for different value of parameters (rate constants). The expression level is either low or high which means that the response is digital in nature in case of binary response. Two distinct subpopulations in a system of genetically identical cell are shown in case of binary response whereas for graded response the unimodal peaks was observed. In second part (3.2) of we describe the transcription factor induced gene. We observe the change of dose response curve that is probability distribution function of induced gene with increased value of Hill coefficient. In third part (3.3) slow and fast kinetics of reaction rate equation are also observed for different rate constants.In fourth section (3.4) we adopt Gillespie model [19] to calculate the protein concentration stochastically. In section (3.5) We observe the effect of rate constants in different aspect of stochastic calculations. As the rate constant increases the noise which arises around mean level of protein concentration with time,decreases. In section (3.6) we study the change in variance, fano factor and mean protein level with rate constants. We have tried to find out the role of different rate constants i.e. protein activation and deactivation rate, protein decay rate, protein degradation rate due to cell growth and dilution rate to cell division, in TF regulated gene expression and also incorporated this in mathematical model of gene expression.

2. Simple Mathematical model of TF regulated gene expression

Transcription factor which basically are the proteins (S) bind at the proper regions of G and regulate its expression of protein. Binding of S with G have a rate k_1,$G + S \xrightarrow{k_1} GS$. Unbinding of S have a rate constant k_2,$GS \xrightarrow{k_2} G + S$, A gene can be eitherin active (G*) state or in inactive (G) state. GS goes to excited state (G*) which have a rate constant k_a and the reverse process has rate constant k_d , $G^* \xrightarrow{k_d} GS$ where$k_a$and k_d are the activation rate constants and the deactivation rate constants respectively. Only in the excited state, gene can synthesis a protein (p) by the rate j_p. The gene degrades with rate constant called$k_p$and the degradation product is given by φ. Proteins can decay irrespective of active and inactive states of gene but protein synthesis occurs only in the active states of gene. The schematic diagram of the translation and transcription are given below

$$G \rightarrow G^* \xrightarrow{j_p} p \xrightarrow{k_p} \varphi$$

$j_p$gives degradation rate due to cell growth andk_p givesdilution rate to cell division. The nature of the transition between active gene to inactive geneis stochastic and given by the following equation

$$G \xrightarrow{k_a} G^*$$
$$G \xleftarrow{k_d} G^*$$

We assume protein synthesis and protein decay occurs deterministically according to the equation

$$\frac{dx}{dt} = \frac{j_p}{X_{max}} z - k_p x$$

where $x = {}^{X}/_{X_{max}}$, X being the protein concentration at time t and X_{max} the maximum protein concentration. The value of z flips between '0' and '1' at random time intervals.In the deterministic approach the time evolution of protein is assumed to be continuous but in real case it is not deterministic as molecular population level changes randomly with time. Deterministic approach is logical when the number of molecules is much more larger than the fluctuating molecule.

The time evolution of the system of reaction is not a continuous process as the molecular population levels in a reaction changes only by discrete amount. Half time for the gene activation is $T_a = \frac{log2}{k_a}$ and the half time for gene deactivation is $T_d = \frac{log2}{k_d}$. The half time associated with the protein degradation is $T_p = \frac{log2}{k_p}$.

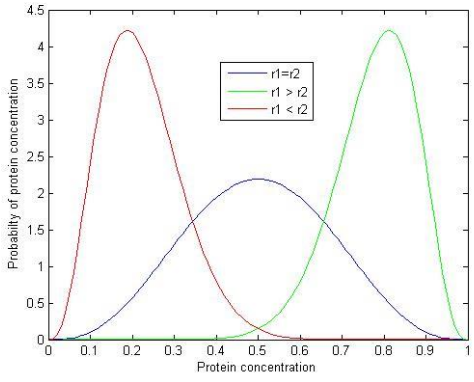
Gillespie Algorithm is used for calculating the gene expression in stochastic process [19]. In this technique concentration of different types of biomolecules are evaluated as a function of time.

In stochastic process the variation of average protein level varies with time which give rise to the noise in the system. The expression of noise or coefficient of variation is given by $(\eta) = \frac{\sigma}{N}$The noise generated in the system can be measured by fano factor also. The fano factor is defined as $(\varphi) = \frac{\sigma^2}{N}$ where N is average protein abundance and σ is standard deviation.

3. Results and Analysis

3.1) Binary and graded Response

The distribution of protein levels in the steady state is given by the probability density function $p(x) = N(1-x)^{r2-1}x^{r1-1}$ where $r_1 = {}^{k_a}/_{k_p}$, $r_2 = {}^{k_d}/_{k_p}$ and $N = \frac{\Gamma(r_1+r_2)}{\Gamma(r_1)\,\Gamma(r_2)}$.Binary and graded response takes place in the same model depending on the value of the parameters $r_1$and r_2. Concentration of Transcription factor with the probability distribution are plotted in Figure1a .When$r_1 < 1$,$r_2 < 1$ bimodal distribution in the protein levels is obtained which is shown in Figure1a. As the concentration (S) of the TF molecules is increased by induced gene expression, a binary response is seen. When r_1 and r_2 both are greater than 1 then the three possible cases are achieved which are shown in Figure1b for three conditions respectively that is, $r_1 > r_2$,$r_2 > r_1$ and$r_1 = r_2$.A single peak is observed which is unimodal distribution with graded response. The peak position shifts with the values of $r_1$and r_2. Peak will be at the middle position when $r_1 = r_2$. When $r_1 > r_2$the peak is shifted towards right and when $r_2 > r_1$the peak is shifted left.



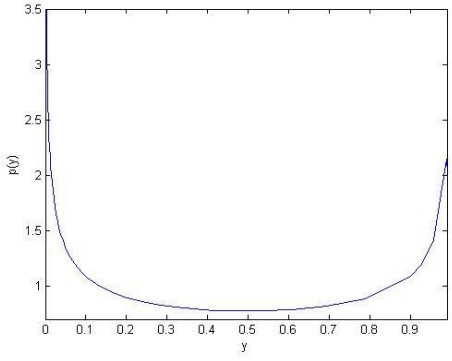


Figure 1: a) binary response in protein level for r1<1 and r2<1 b)Protein concentration changes withProbability distribution function give graded response for different rate constants r_1 and r_2.

In the binary gene expression when the gene is in inactive state, the mean protein level (x) will be zero and when it is in active state the mean protein level will be one,X will becomeX_{max} i.e the maximum protein synthesis. Two distinct subpopulations originate due to slow transitions between the inactive and active states of the gene.$k_a$and k_d will be the function of concentration (S) of TF moleculesif TF influences the transition from G to G* then. The fraction of cell goes to high state from lower onedue to the increse of activator molecule.We have taken k_a = 1 and k_d=2 for our analysis If the rate of protein decy is more than the activation and deactivation rate constants mean protein level will be either high or at low state, depending on whether the gene is in activated or deactivated state. If the residence time of gene in activated state is sufficient, protein expression will be maximum and hence high state is achieved. If the gene is in deactivated state for a sufficiently long time all the accumulated protein decays fully and it goes to low state.

3.2) Effect of rate constant and Hill coefficient inTF regulated gene expression

In our previous paper [9] it had been shown that effective rate constants vary with concentration of TF. The Dose response curve was sigmoid which gives the maximum steepness at intermediate level. A little change in the concentration of TF about the inflection point, gave wide change of effective rate of protein synthesis. Inducer increased the number of expressed cell but the not the average protein concentration.

Figure 2 shows the variation of probability distribution function with the change of concentration of TF. It is seen from the graph that with the increasing value of hill coefficient effective rate constant changes. These gives a increasing peak value of PDF. For largerer value of n (n=13) peak height is high. For n=7, the peak of the distribution function decreases and shifts towards left. As hill coefficient is low (n=4) the peak height becones less.

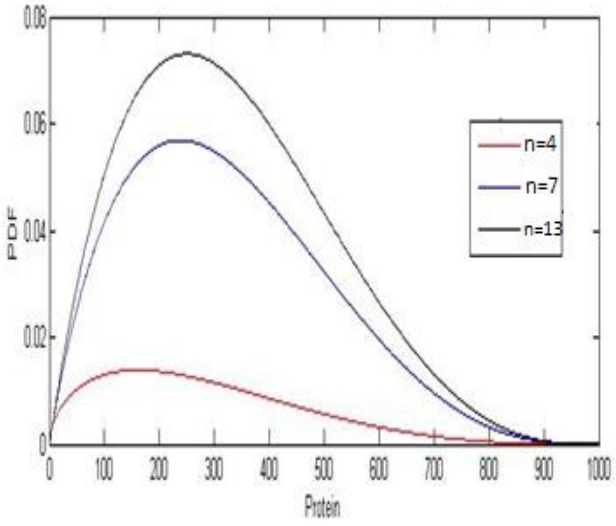


Figure 2 Protein concentration vs. PDF for three different value of hill function

3.3) Slow and fast kinetics

Let $\boldsymbol{T_a = T_d = {}^{T_p}/_{\gamma}}$ so $\boldsymbol{k_a = \frac{log2}{T_a}}$ and $\boldsymbol{k_d = \frac{log2}{T_d}}$ and $\boldsymbol{k_p = \frac{log2}{T_p} = \frac{log2}{\gamma T_a}}$=$\boldsymbol{\alpha k_a}$where $\boldsymbol{\alpha}$ and $\boldsymbol{\gamma}$ are numeric constant and $\boldsymbol{\alpha}$ is always positive.In Figure 3 we plot the. protein concentration vs. PDF for slow and fast kinetics. As $\boldsymbol{\alpha}$ increases the gene expression kinetics become faster but the peak of mean protein level remains in the same position of the protein level.

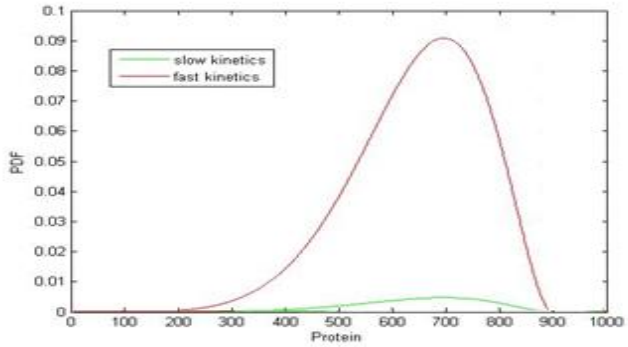


Figure3: slow and fast kinetics occurs for different rate constants

3.4) Effect of rate constant in stochastic gene expression

Gillespie model [19] is used as the Mathematical model of gene expression.The time evolution of average protein and average protein concentration histogram is ploted in Figure 4a and Figure4b. Histogram shows the unimodal distribution which can also seen in deterministic process (Figure 1b, 2 and 3).

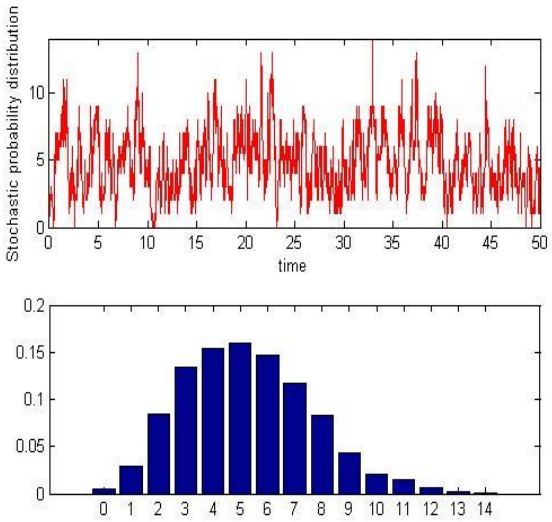


Figure 3(a): Time evolution of concentration of protein about mean level

(3b) Hitogram depicts Unimodal distribution of protein level

3.5) Effect of noise in gene expression

Noise plays an important role in gene expression. Amount of protein expressed randomly is always fluctuate around a mean value. Random fluctuation around the mean protein level gives rise to noise in the stochastic analysis is observed clearly in Figure 4a.In Figure 4b the rate constant is increased ten times. It reduces noise which is seen clearly in Figure 4b which proves the rate constants have a important role in case of stochastic in gene expression. This happens due to the increase in protein dissociation with the increase of rate constants.

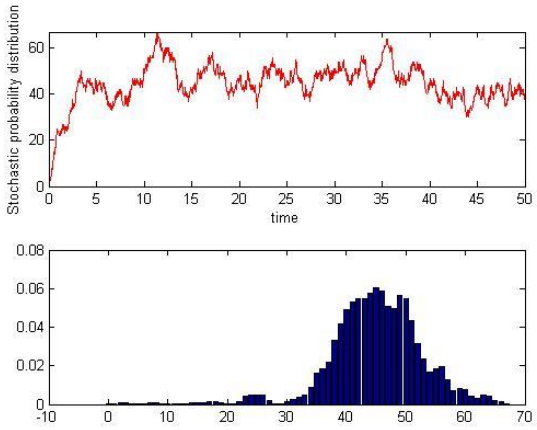


Figure4a,b: As the rate constant increases from 0.06 (4a) to 0.6 (4b) randomness also decreases

In figure 5 we plot average protein concentration with time using deterministic method for different rate constants. We plot for three different rate constants k=0.06, 0.6 and 6. For higher rate constant (k=6) the syatem reaches to equilibrium more faster rate.

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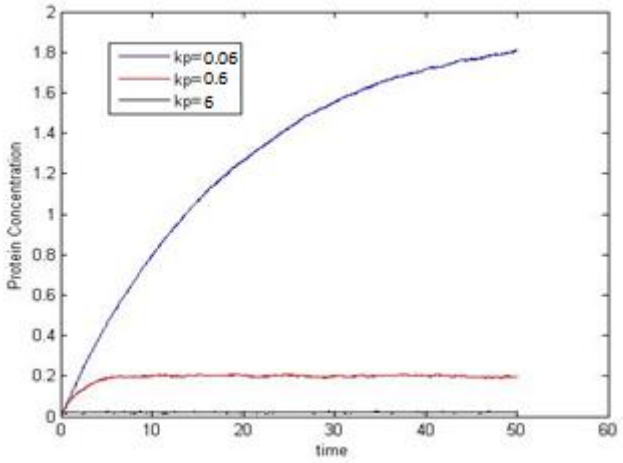

Figure 5: For different rate constants protein concentration with time are plotted.

The significance of this behaviour shown in Figure 5 is that for low activation rate the gene get more time to stay in inactive state so time requires to reach equillibrium is also slower.These fluctuation of noise is calculated by fanofactor.The data of Table1 shows that with increasing value of k_p (for a fixed value of j_p) variance decreases i.e. noise is less which is also evident from Figure 4. The fano factor decreases with increasing value of k_p. For a fixed value of k_p variance, fanofactor and mean protein level increases. Table1 shows the how rate constants k_p and j_p are related with variance and noise.

Table 1:The dependence of mean protein level, variance and fano factor with different k_p and j_p values

j_p	k_p	Variance	Fano-factor	Mean protein level
30	0.06	1.00×10^4	25	405
	0.6	60.33	1.3	47
	6	4.4	0.9	5
90	0.06	1.79×10^5	110.1	1645

	0.6	511	2.6	200
	6	20.37	0.9	21
900	0.06	1.88×10^7	1135	16800
	0.6	1.97×10^5	15.1	2500
	6	229.55	1.2	200

In Figure 6 we plot the change of variance with average protein concentration. It is evident from the plot that variance increases linearly with average protein concentration.

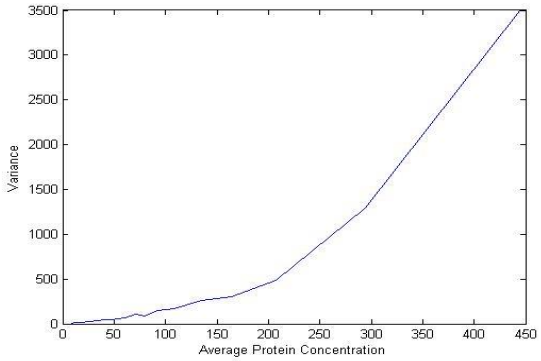

Figure 7: Change in variance with average protein concentration

We calculate the variance in protein concentration from the stochastic model of Gillespie for different rate constant. In deterministic cases we get the same time dependence with rate constant .With the increase of rate constant variance increases and reaches a peak for a particular value of k_p (k_p=1.6) evident from the table, after that with the increase of rate constant variance decreases.

Table 2: Rate constants k_p vs variance

Rate constants (k_p)	Variance $(\eta) = \frac{\sigma}{N}$
1	4500
1.6	9500
2	5000
2.5	2000
3.5	1000

4. Conclusion

. Simple mathematical model of gene expression is studied in deternistic and stochastic way. We assume that activation and of gene in excited state is a random process but protein synthesis and protein decay are deterministic in nature where number of protein molecule expressed are quite large. Binary and graded response are observed in the same syatem for different values of rate constants (r1and r2). When TF molecules are joined in the promoter region then gene becomes activated and emits protein. This TF regulated gene expressions are also controlled by typical rate constants. The rate of reaction can be made faster or slower by choosing particular rate constants. Stochastic gene expression and protein concentration is calculated by Gillespie algorithm. Stochastic method also has a dependence on deterministic rate constants. Stochasticity decreases with increasing value of rate constants. Unimodal distribution of histogram verifies the deterministic approach. Equillibrium also reaches earlier by increasing rate constants. Fano factor and variances are calculated for different rate constants. In our paper we observe the deterministic and stochastic approach both gives the same result and both have dependence on rate constants in case of TF regulated gene expression.

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